METHODS AND COMPOSITIONS FOR TREATING OR PREVENTING PSYCHIATRIC DISORDERS WITH COX-2 INHIBITORS ALONE AND IN COMBINATION WITH ANTIDEPRESSANT AGENTS

BACKGROUND OF THE INVENTION

(1) Field of the Invention:

[0001] The present invention relates generally to the use of an enzyme inhibitor alone and in combination with an antidepressant agent for the treatment or prevention of psychiatric disorders, and in particular to the use of a cyclooxygenase-2 inhibitor alone and in combination with an antidepressant agent.

(2) Description of the Related Art:

[0002] Many people in the United States and around the world suffer from some form or combination of psychiatric disorders. A broad spectrum of psychiatric disorders has now been recognized, many of which have overlapping and interacting etiologies. Two of the most widespread and prevalent of the psychiatric disorders are depression (uni-polar disorder or major depressive disorder) and manic depression (bi-polar disorder).

[0003] The most common category of psychiatric disorders is mood disorders, accounting for 25% of patients in public mental institutions, 65% of psychiatric outpatients, and 10% of all patients seen in nonpsychiatric medical settings. Mood disorders are a group of typically recurrent illnesses characterized by pervasive disturbances, psychomotor dysfunction and vegetative symptoms, including depression, manic depression, dysthymic disorders, and cyclothymic disorder. Some type of mood disorder affects 20% of women and 12% of men during their lifetime, with a major part of these figures representing subjects suffering from depression. See *The Merck Manual of Diagnosis & Therapy, Beers & Brakow, 17th edition,* Published by Merck Research Labs, *Sec. 15, Chap. 189, Psychiatric Disorders, Mood Disorders* (1999).

[0004] A subject suffering from depression may display a variety of symptoms and moods. The mood of a subject suffering from depression can generally be depressed, irritable, anxious, miserable, morbid, preoccupied with guilt, self-degenerating, indecisive, helpless, hopeless, or any combination thereof. The subject may also have social withdrawal, recurrent thoughts of death or suicide, sleep disorders, decreased ability to concentrate, diminished interest in usual activities, or any combination of these symptoms.

[0005] While the exact cause of depression and other mood disorders is unknown, it has been suggested that impaired limbic-diencephalic function is the final pathway causing mood disorders. Also, cholinergic, catecholaminergic (noradrenergic or dopaminergic) and serotonergic (5-HT) neurotransmission imbalances have been implicated as a cause of many mood disorders. Most antidepressant agents are directed toward these systems as a treatment or prevention of psychiatric disorders.

[0006] Other causes of mood disorders can be stressors that provoke affective episodes either psychologically or biologically. Traumatic life events, especially separations, commonly precede depressive and manic depressive episodes. This type of mood disorder may arise in a subject with any type of personality, although, such events may trigger depression symptoms from manifesting in a subject suffering from a subtle mood disorder rather than its cause.

[0007] Some subjects suffering from one or more psychiatric disorders also have signs of physical pain, sickness, headaches, or other physical conditions. Subjects diagnosed with one or more psychiatric disorders are often treated as outpatients, although other patients require full-time supervision and treatment. Antidepressant agents play a large role in this treatment, usually in combination with supportive therapy. Many different types of antidepressant agents with varying functionalities have emerged over the years and are used as pharmaceutical therapies. See Ables, A., et al., Am. Fam. Physician 67(3):547-54 (2003). These

antidepressant agents are helpful to the patient by helping to treat and prevent the emergence of symptoms associated with the psychiatric disorder. See Hegarty K. et al., Aust. Fam. Physician 32(4):229-34, 236-7, 239 (2003). In fact, symptom remission is usually the goal of treatment of a subject suffering from a psychiatric disorder.

[0008] An example of one of the most prevalently prescribed antidepressant agents is the compound sertraline (Zoloft®). Sertraline was initially introduced for the treatment of depression, but it is now used to treat a wide variety of psychiatric disorders. See Khouzam H., *et al., Compr. Ther. 29(1)*:47-53 (2003). Sertraline acts as a selective serotonin reuptake inhibitor (SSRI). However, it is structurally unrelated to other SSRIs, tricyclic, tetracyclic, or other available antidepressant agents.

[0009] Even after treatment with an antidepressant agent, a subject suffering from depression often continues to have symptoms. See Menza M., *et al., J. Clin. Psychiatry 64(5)*:516-23 (2003).

[0010] Some subjects also develop physical side effects during treatment with an antidepressant agent. These side effects may include sexual dysfunction, sickness, headaches, pain, sleep disorders, physical dependence and addiction to the antidepressant agent, and other adverse side effects. Also, many subjects suffering from depression do not respond as expected to conventional treatment with antidepressant drugs.

[0011] Moreover, the treatment of psychiatric disorders with only antidepressant agents fails to address all the underlying causes of psychiatric disorders. This is problematic because some psychiatric disorders are thought to arise, in part, from the release of inflammatory mediators formed within the brain. For example, several clinical studies have suggested that depression may be accompanied by an activation of the inflammatory response system. See Tiemeier, H., et *al., Epidemiology 14(1)*:103-7 (2003). Another study reported that an association exists between depression and the presence of low-grade systemic inflammation. See Danner, M., *et al., Psychosom. Med. 65(3)*:347-56

(2003). Conventional antidepressants fail to address this inflammatory aspect of psychiatric disorders.

[0012] Inhibitors of the cyclooxygenase-2 (Cox-2) enzyme have been increasingly recognized as having beneficial effects on inflammation. For example, typical of the development of many inflammatory symptoms is upregulation of the Cox-2 enzyme. Cox-2 is an enzyme produced by an inducible gene, which is responsible for the biosynthesis of prostaglandins in inflammatory cells. Inflammation causes the induction of the Cox-2 enzyme, leading to the release of prostanoids (prostaglandin E2), which sensitize peripheral nociceptor terminals and produce localized inflammation and edema. *See e.g.,* Samad, T., *et al., Nature 410*(6827):471-5 (2001).

[0013] Historically, physicians have treated inflammation-related disorders with a regimen of nonsteroidal anti-inflammatory drugs (NSAIDS), such as, for example, aspirin and ibuprofen. Undesirably, however, some NSAIDS are known to cause gastrointestinal (GI) bleeding or ulcers in patients undergoing consistent long term regimens of NSAID therapy. See Henry, D., *et al., Lancet 337*:730 (1991).

[0014] A reduction of unwanted side effects of common NSAIDS was made possible by the discovery that two cyclooxygenases are involved in the transformation of arachidonic acid as the first step in the prostaglandin synthesis pathway. These enzymes exist in two forms and have been termed cyclooxygenase-1 (Cox-1) and cyclooxygenase-2 (Cox-2). See Needleman, P. *et al., J. Rheumatol. 24, Suppl. 49*:6-8 (1997).

[0015] Cox-1 is a constitutive enzyme responsible for the biosynthesis of prostaglandins in the gastric mucosa and in the kidney. Cox-2 is an enzyme that is produced by an inducible gene that is responsible for the biosynthesis of prostaglandins in inflammatory cells. Inflammation causes the induction of Cox-2, leading to the release of prostanoids (prostaglandin E2), which sensitize peripheral nociceptor terminals and produce localized pain hypersensitivity, inflammation, and oedema. See Samad, T., *et al., Nature 410(6827)*:471-5 (2001).

[0016] Many common NSAIDs are now known to be inhibitors of both Cox-1 and Cox-2. Accordingly, when administered in sufficiently high levels, these NSAIDs not only alleviate the inflammatory consequences of Cox-2 activity, but also inhibit the beneficial gastric maintenance activities of Cox-1.

[0017] Research into the area of arachidonic acid metabolism has resulted in the discovery of compounds that selectively inhibit the Cox-2 enzyme to a greater extent than the activity of Cox-1. The Cox-2 selective inhibitors are believed to offer advantages that include the capacity to prevent or reduce inflammation while avoiding harmful side effects associated with the inhibition of Cox-1. Thus, Cox-2 selective inhibitors have shown great promise for use in therapies -- especially in therapies that require maintenance administration, such as for pain and inflammation control.

[0018] While Cox-2 inhibitors have been described heretofore for treating pain and inflammation, they have not been described for the treatment or prevention of psychiatric disorders.

[0019] Despite the recent advances that have been made in understanding psychiatric disorders, they remain notoriously difficult to treat or prevent. Although significant progress has been made in the field of antidepressant agents, a continuing need still exists for better antidepressant agents that also have fewer side-effects and a more targeted functionality. From the foregoing, it can be seen that a need exists for improved methods and therapeutic compositions to treat psychiatric disorders. It would also be useful to provide an improved method and composition for reducing the symptoms associated with psychiatric disorders. Likewise, methods and compositions that improve patient outcomes following treatment with antidepressant agents would be desirable. Also, methods and compositions that reduce dosages or reduce unwanted side effects in conventional treatments for psychiatric disorders are desirable. Finally, methods and compositions that improve the efficacy of treating psychiatric disorders that are resistant in a

particular subject to known methods of therapy alone would also be desirable.

SUMMARY OF THE INVENTION

[0020] Briefly, therefore, the present invention is directed to a novel method of treating or preventing a psychiatric disorder in a subject comprising administering to the subject at least one Cox-2 inhibitor.

[0021] The present invention is also directed to a novel method of treating or preventing a psychiatric disorder in a subject comprising administering to the subject at least one Cox-2 inhibitor in combination with an antidepressant agent.

[0022] The present invention is also directed to a novel therapeutic composition comprising a Cox-2 inhibitor and an antidepressant agent.

[0023] The present invention is also directed to a novel pharmaceutical comprising a Cox-2 inhibitor, an antidepressant agent, and a pharmaceutically acceptable carrier.

[0024] The present invention is also directed to a novel kit for preventing or treating psychiatric disorders in a subject that is in need of such prevention or treatment, the kit comprising one dosage form comprising a Cox-2 inhibitor and a second dosage form comprising an antidepressant agent.

[0025] Among the several advantages found to be achieved by the present invention, therefore, may be noted the provision of improved methods, therapeutic compositions, pharmaceutical compositions, and kits for the prevention or treatment of psychiatric disorders such as depression. Other advantages achieved by the present invention include improved methods, compositions, and kits for reducing both the inflammation and depression symptoms that may be associated with psychiatric disorders. Still other advantages achieved by the present invention include methods, compositions, and kits that improve patient recurrences of psychiatric symptoms. In addition, the present invention provides methods, compositions, and kits that reduce dosages or reduce

unwanted side effects in conventional treatments for psychiatric disorders. Finally, the present invention provides methods and compositions that improve the efficacy of treating a psychiatric disorder that is considered resistant or intractable to known methods of therapy alone.

DETAILED DESCRIPTION

[0026] In accordance with the present invention, it has been discovered that the treatment and/or prevention of psychiatric disorders, including such disorders as depression and manic depression, is provided by a therapy comprising a Cox-2 inhibitor alone or in combination with an antidepressant agent.

[0027] For purposes of the present invention, the novel therapy comprising at least one Cox-2 inhibitor alone or in combination with at least one antidepressant agent is useful for the purpose of preventing or treating psychiatric disorders. The present therapy is also useful for the purpose of preventing or treating psychiatric disorders in a subject that is in need of such prevention or treatment.

[0028] The therapy of the present invention is useful, for example, to reduce such psychiatric disorder symptoms as a mood that is depressed, irritable, anxious, miserable, morbid, preoccupied with guilt, self-degenerating, indecisive, helpless, hopeless, or any combination of the foregoing. The subject may also have social withdrawal, recurrent thoughts of death or suicide, sleep disorders, decreased ability to concentrate, diminished interest in usual activities, or any combination of these symptoms. The therapy of the present invention would also be useful to prevent the occurrence of such symptoms.

[0029] The methods and compositions of the present invention are also useful to reduce the number of hospitalizations of subjects suffering from a chronic psychiatric disorder.

[0030] The administration of a Cox-2 inhibitor alone or in combination with at least one antidepressant agent for the prevention or treatment of a psychiatric disorder is an unexpectedly effective treatment

and preventative therapy. Such administration is effective for improving the symptoms of a psychiatric disorder while avoiding or reducing certain disadvantages of current treatments. The therapy of a Cox-2 inhibitor alone or in combination with at least one antidepressant agent is also useful for decreasing the required number of separate dosages, thus, potentially improving patient compliance.

[0031] Therapies comprising at least one Cox-2 inhibitor alone or in combination with at least one antidepressant agent are useful not only for improving psychiatric disorder symptoms and shortening recovery times, but also for reducing or eliminating the dosages of antidepressant agents that are normally required. The elimination of or administration of lower dosages of antidepressant agents provides a reduction in side effects corresponding to such antidepressant agents.

[0032] Another embodiment of the present invention is a combination therapy for treating or preventing psychiatric disorders and psychiatric disorder symptoms in a subject in need of such treatment and prevention comprising at least one Cox-2 inhibitor and at least one antidepressant agent.

[0033] Such administration is effective for improving the symptoms of psychiatric disorders while avoiding or reducing certain disadvantages of current treatments. The combination therapy of a Cox-2 inhibitor and an antidepressant agent is also useful for decreasing the required number of separate dosages, thus, potentially improving patient compliance. For example, in one embodiment, the combination therapy of the present invention is useful for reducing the dosing frequency of conventional antidepressant treatment agents. One antidepressant agent, buproprion (Wellbutrin®), is typically dosed three to four times daily. Dosing three to four times daily may become problematic for a subject suffering from a neurodegenerative symptom, such as short term memory loss or from seriously ill subjects who have difficulty complying with multiple doses/day. Thus, administering the combination therapy of the present invention to a

subject undergoing dosing with buproprion may reduce the required number of separate doses normally prescribed with buproprion.

[0034] Combination therapies comprising Cox-2 inhibitors and antidepressant agents are useful not only for improving psychiatric disorder symptoms and shortening recovery times, but also for reducing the dosages of conventional antidepressant agents that are normally required.

[0035] For example, the combination therapy is effective for lowering the dosages of antidepressant agents that are normally prescribed as a monotherapy. The administration of lower dosages of antidepressant agents provides a reduction in side effects corresponding to such agents. Reduced dosages of antidepressant agents are beneficial where normal dosages often exhibit harmful side effects, for example, with such conventional antidepressant agents as fluoxetine (Prozac®). In some patients, fluoxetine causes sexual dysfunction, which can lead to reduced patient compliance with the treatment regimen.

[0036] The administration of a Cox-2 inhibitor in combination with an antidepressant agent is an effective treatment for psychiatric disorders and psychiatric disorder-related symptoms, and in preferred embodiments, is superior to the use of either agent alone.

[0037] Moreover, in one embodiment, the combination therapy demonstrates a synergistic efficacy for treating and preventing psychiatric disorders and psychiatric disorder-related complications that is greater than what would be expected from simply combining the two therapies.

[0038] The term "synergistic" refers to the combination of a Cox-2 inhibitor and an antidepressant agent as a combined therapy having an efficacy for the prevention and treatment of psychiatric disorders that is greater than what would be expected merely from the sum of their individual effects.

[0039] The synergistic effects of the embodiments of the present invention's combination therapy encompass additional advantages for the treatment and prevention of psychiatric disorders. Such additional

advantages include, but are not limited to, lowering the required dose of antidepressant agents, reducing the side effects of antidepressant agents, and rendering those agents more tolerable to subjects in need of psychiatric disorder therapy.

[0040] As used herein, the phrases "combination therapy", "co-administration", “co-administering”, “administration with”, “administering”, “combination”, or "co-therapy", when referring to the embodiment of the present invention that comprises the use of a Cox-2 inhibitor in combination with an antidepressant agent, are intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner. Thus, the Cox-2 inhibitor and antidepressant agent may be administered in one therapeutic dosage form, such as in a single capsule, tablet, or injection, or in two separate therapeutic dosage forms, such as in separate capsules, tablets, or injections.

[0041] Sequential administration of such treatments encompasses both relatively short and relatively long periods between the administration of each of the drugs of the present method. However, for purposes of the present invention, the second drug is administered while the first drug is still having an efficacious effect on the subject.

[0042] Preferably, the second of the two drugs is to be given to the subject within the therapeutic response time of the first drug to be administered. For example, the combination therapy of the present invention encompasses administration of a Cox-2 inhibitor to the subject and the later administration of an antidepressant agent, as long as the antidepressant agent is administered to the subject while the Cox-2 inhibitor is still present in the subject at a level, which in combination with the level of the antidepressant agent is therapeutically effective, and vice versa.

[0043] As used herein, the term "therapeutic response time" means the duration of time that a compound is present or detectable within a subject's body at therapeutic concentrations.

[0044] As used herein, the term "monotherapy" is intended to embrace administration of a Cox-2 inhibitor to a subject suffering from a psychiatric disorder as a single therapeutic treatment without any additional therapeutic treatment comprising an antidepressant agent. However, the Cox-2 inhibitor may still be administered in multiple dosage forms. Thus, the Cox-2 inhibitor may be administered in one therapeutic dosage form, such as in a single capsule, tablet, or injection, or in two separate therapeutic dosage forms, such as in separate capsules, tablets, or injections.

[0045] In one embodiment, the present invention provides a method for treating or preventing psychiatric disorders in a subject in need of such treatment or prevention.

[0046] In another embodiment, the present invention provides a method for preventing psychiatric disorders in a subject comprising administering to the subject a Cox-2 inhibitor alone or in combination with an antidepressant agent.

[0047] As used herein, the terms "to prevent", "preventing", or "prevention" refer to any reduction, no matter how slight, of a subject's predisposition or risk for developing a psychiatric disorder. This definition includes either preventing the onset of a psychiatric disorder altogether or preventing the onset of a preclinically evident stage of a psychiatric disorder in individuals at risk.

[0048] In yet another embodiment, the present invention provides a method for treating psychiatric disorders in a subject comprising administering to the subject a Cox-2 inhibitor alone or in combination with an antidepressant agent.

[0049] As used herein, the terms "treating", "treatment", "treated", or "to treat," mean to alleviate symptoms, eliminate the cause of symptoms either on a temporary or permanent basis, or to alter or slow the

appearance of symptoms or symptom worsening. The term "treatment" includes alleviation or elimination of the cause of the symptoms associated with, but not limited to, any of the psychiatric disorders or psychiatric disorder-related symptoms described herein.

[0050] Without being bound by this or any other theory, it is believed that a therapy comprising a Cox-2 inhibitor alone or in combination with an antidepressant agent is efficacious for preventing or treating psychiatric disorders and psychiatric disorder-related symptoms.

[0051] The combination therapy embodiment of the present invention also provides for the treatment of psychiatric disorder-related symptoms, which may arise indirectly from having a psychiatric disorder, by treating the underlying psychiatric disorder itself. For example, if a subject is suffering from a psychiatric disorder-related symptom, such as a depressed mood, the treatment of the underlying psychiatric disorder, such as depression, by the methods and compositions of the present invention will likewise improve the symptoms of the associated complication.

[0052] The present invention encompasses a novel method of preventing or treating psychiatric disorders and psychiatric disorder-related symptoms in a subject that is in need of such prevention or treatment comprising administering to the subject at least one Cox-2 inhibitor. In a second embodiment, the present invention encompasses a novel method of preventing or treating psychiatric disorders and psychiatric disorder-related symptoms in a subject that is in need of such prevention or treatment comprising administering to the subject at least one Cox-2 inhibitor and one or more antidepressant agents.

[0053] A component of the present invention is a Cox-2 inhibitor.

[0054] Inhibitors of the cyclooxygenase pathway in the metabolism of arachidonic acid used in the prevention and treatment of psychiatric disorders may inhibit enzyme activity through a variety of mechanisms. By the way of example, the inhibitors used in the methods described herein

may block the enzyme activity directly by acting as a substrate for the enzyme.

[0055] The terms "cyclooxygenase-2 inhibitor", or "Cox-2 inhibitor", which can be used interchangeably herein, embrace compounds which inhibit the Cox-2 enzyme regardless of the degree of inhibition of the Cox-1 enzyme, and include pharmaceutically acceptable salts of those compounds. Thus, for purposes of the present invention, a compound is considered a Cox-2 inhibitor irrespective of whether the compound inhibits the Cox-2 enzyme to an equal, greater, or lesser degree than the Cox-1 enzyme.

[0056] In one embodiment of the present invention, it is preferred that the Cox-2 inhibitor compound is a non-steroidal anti-inflammatory drug (NSAID). Therefore, preferred materials that can serve as the Cox-2 inhibitor of the present invention include non-steroidal anti-inflammatory drug compounds, a pharmaceutically acceptable salt thereof, or a pure (-) or (+) optical isomeric form thereof.

[0057] Examples of NSAID compounds that are useful in the present invention include acemetacin, acetyl salicylic acid, alclofenac, alminoprofen, azapropazone, benorylate, benoxaprofen, bucloxic acid, carprofen, choline magnesium trisalicylate, clidanac, clopinac, dapsone, diclofenac, diflunisal, droxicam, etodolac, fenoprofen, fenbufen, fenclofenec, fentiazac, floctafenine, flufenisal, flurbiprofen, (r)-flurbiprofen, (s)-flurbiprofen, furofenac, feprazone, flufenamic acid, fluprofen, ibufenac, ibuprofen, indometacin, indomethacin, indoprofen, isoxepac, isoxicam, ketoprofen, ketorolac, miroprofen, piroxicam, meloxicam, mefenamic, mefenamic acid, meclofenamic acid, meclofen, nabumetone, naproxen, niflumic acid, oxaprozin, oxipinac, oxyphenbutazone, phenylbutazone, podophyllotoxin derivatives, proglumetacin, piprofen, pirprofen, prapoprofen, salicylic acid, salicylate, sudoxicam, suprofen, sulindac, tenoxicam, tiaprofenic acid, tiopinac, tioxaprofen, tolfenamic acid, tolmetin, zidometacin, zomepirac, and 2-fluoro-a-methyl[1,1'-biphenyl]-4-acetic acid, 4-(nitrooxy)butyl ester.

[0058] In a preferred embodiment, the Cox-2 inhibitor is a Cox-2 selective inhibitor. The term "Cox-2 selective inhibitor" embraces compounds which selectively inhibit the Cox-2 enzyme over the Cox-1 enzyme, and also include pharmaceutically acceptable salts and prodrugs of those compounds.

[0059] In practice, the selectivity of a Cox-2 inhibitor varies depending upon the condition under which the test is performed and on the inhibitors being tested. However, for the purposes of this specification, the selectivity of a Cox-2 inhibitor can be measured as a ratio of the in vitro or in vivo IC50 value for inhibition of Cox-1, divided by the IC50 value for inhibition of Cox-2 (Cox-1 IC50/Cox-2 IC50). A Cox-2 selective inhibitor is any inhibitor for which the ratio of Cox-1 IC50 to Cox-2 IC50 is greater than 1. In preferred embodiments, this ratio is greater than 2, more preferably greater than 5, yet more preferably greater than 10, still more preferably greater than 50, and more preferably still greater than 100.

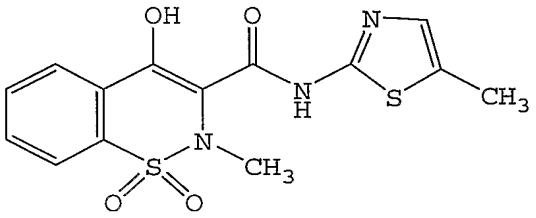
[0060] As used herein, the term "IC50" refers to the concentration of a compound that is required to produce 50% inhibition of cyclooxygenase activity. Preferred Cox-2 selective inhibitors of the present invention have a Cox-2 IC50 of less than about 1 μM, more preferred of less than about 0.5 μM, and even more preferred of less than about 0.2 μM.

[0061] Preferred Cox-2 selective inhibitors have a Cox-1 IC50 of greater than about 1 μM, and more preferably of greater than 20 μM. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

[0062] Also included within the scope of the present invention are compounds that act as prodrugs of Cox-2-selective inhibitors. As used herein in reference to Cox-2 selective inhibitors, the term "prodrug" refers to a chemical compound that can be converted into an active Cox-2 selective inhibitor by metabolic or simple chemical processes within the body of the subject. One example of a prodrug for a Cox-2 selective inhibitor is parecoxib, which is a therapeutically effective prodrug of the tricyclic Cox-2 selective inhibitor valdecoxib. An example of a preferred

Cox-2 selective inhibitor prodrug is sodium parecoxib. A class of prodrugs of Cox-2 inhibitors is described in U.S. Patent No. 5,932,598.

[0063] The Cox-2 selective inhibitor of the present invention can be, for example, the Cox-2 selective inhibitor meloxicam, Formula B-1 (CAS registry number 71125-38-7), or a pharmaceutically acceptable salt or prodrug thereof.



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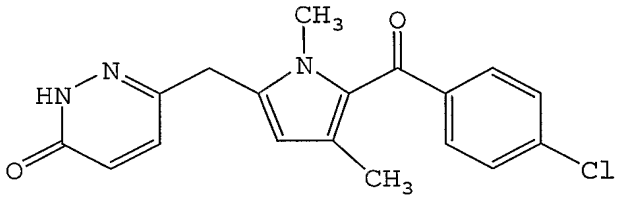
[0064] In another embodiment of the invention the Cox-2 selective inhibitor can be the Cox-2 selective inhibitor RS 57067, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, Formula B-2 (CAS registry number 179382-91-3), or a pharmaceutically acceptable salt or prodrug thereof.



B-2

[0065] As used herein, the term "alkyl", either alone or within other terms such as "haloalkyl" and "alkylsulfonyl"; embraces linear or branched radicals having one to about twenty carbon atoms. Lower alkyl radicals have one to about ten carbon atoms. The number of carbon atoms can also be expressed as "C_1-C_5", for example. Examples of lower alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, hexyl, octyl and the like.

[0066] The term "alkenyl" refers to an unsaturated, acyclic hydrocarbon radical, linear or branched, in so much as it contains at least

one double bond. The alkenyl radicals may be optionally substituted with groups such as those defined below. Examples of suitable alkenyl radicals include propenyl, 2-chloropropylenyl, buten-1yl, isobutenyl, penten-1yl, 2-methylbuten-1-yl, 3-methylbuten-1-yl, hexen-1-yl, 3-hydroxyhexen-1-yl, hepten-1-yl, octen-1-yl, and the like.

[0067] The term "alkynyl" refers to an unsaturated, acyclic hydrocarbon radical, linear or branched, in so much as it contains one or more triple bonds, such radicals preferably containing 2 to about 6 carbon atoms, more preferably from 2 to about 3 carbon atoms. The alkynyl radicals may be optionally substituted with groups such as described below. Examples of suitable alkynyl radicals include ethynyl, propynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 4-methoxypentyn-2-yl, 3-methylbutyn-1-yl, hexyl-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl radicals, and the like.

[0068] The term "oxo" means a single double-bonded oxygen.

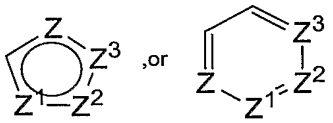
[0069] The terms "hydrido", "-H", or "hydrogen", denote a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical, or two hydrido radicals may be attached to a carbon atom to form a methylene ($-CH_2-$) radical.

[0070] The term "halo" means halogens such as fluorine, chlorine, and bromine or iodine atoms. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl, and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have a bromo, chloro, or a fluoro atom within the radical. Dihalo alkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals.

[0071] The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals.

[0072] The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro, or bromo, to provide "haloalkoxy" or "haloalkoxyalkyl" radicals. Examples of "alkoxy" radicals include methoxy, butoxy, and trifluoromethoxy.

[0073] The term "aryl", whether used alone or with other terms, means a carbocyclic aromatic system containing one, two, or three rings wherein such rings may be attached together in a pendent manner, or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronapthyl, indane, and biphenyl. The term "heterocyclyl" means a saturated or unsaturated mono- or multi-ring carbocycle wherein one or more carbon atoms are replaced by N, S, P, or O. This includes, for example, structures such as:



where Z, Z^1, Z^2, or Z^3 is C, S, P, O, or N, with the proviso that one of Z, Z^1, Z^2, or Z^3 is other than carbon, but is not O or S when attached to another Z atom by a double bond or when attached to another O or S atom. Furthermore, the optional substituents are understood to be attached to Z, Z^1, Z^2, or Z^3 only when each is C. The term "heterocycle" also includes fully saturated ring structures, such as piperazinyl, dioxanyl, tetrahydrofuranyl, oxiranyl, aziridinyl, morpholinyl, pyrrolidinyl, piperidinyl, thiazolidinyl, and others.

[0074] The term "heteroaryl" embraces unsaturated heterocyclic radicals. Examples of unsaturated heterocyclic radicals include thienyl, pyrryl, furyl, pyridyl, pyrimidinyl, pyrazinyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, pyranyl, and tetrazolyl. The term also embraces

radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like.

[0075] The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$. "Alkylsulfonyl", embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. The term "arylsulfonyl" embraces sulfonyl radicals substituted with an aryl radical. The term "aminosulfonyl" denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide ($-SO_2-NH_2$).

[0076] The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2-H$. The term "carboxyalkyl" embraces radicals having a carboxyradical as defined above, attached to an alkyl radical. The term "carbonyl", whether used alone or with other terms, such as "alkylcarbonyl", denotes – (C=O) –. The term "alkylcarbonyl" embraces radicals having a carbonyl radical substituted with an alkyl radical. An example of an "alkylcarbonyl" radical is CH_3 – (CO) –. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl (C=O) radical. Examples of such "alkoxycarbonyl" radicals include $(CH_3)_3$-C-O–C=O) – and – (O=)C– OCH_3. The term "amino", whether used alone or with other terms, such as "aminocarbonyl", denotes $-NH_2$.

[0077] The term "heterocycloalkyl" embraces heterocyclic-substituted alkyl radicals such as pyridylmethyl and thienylmethyl. The terms "aralkyl", or "arylalkyl" embrace aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, and diphenylethyl. The terms benzyl and phenylmethyl are interchangeable. The term "cycloalkyl" embraces radicals having three to ten carbon atoms, such as cyclopropyl cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. The term "cycloalkenyl" embraces unsaturated radicals having three to ten carbon

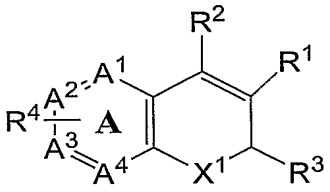
atoms, such as cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, and cycloheptenyl.

[0078] The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. An example of "alkylthio" is methylthio, (CH_3 –S–). The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent –S(–O) – atom. The term "acyl", whether used alone, or within a term such as "acylamino", denotes a radical provided by the residue after removal of hydroxyl from an organic acid.

[0079] The term "cyano", used either alone or with other terms, such as "cyanoalkyl", refers to C≡N. The term "nitro" denotes –NO_2.

[0080] In one embodiment of the invention the Cox-2 selective inhibitor is of the chromene/chroman structural class, which encompasses substituted benzopyrans or substituted benzopyran analogs, as well as substituted benzothiopyrans, dihydroquinolines, or dihydronaphthalenes having the structure of any one of the general Formulas I, II, III, IV, V, and VI, shown below, and including, by way of non-limiting example, the structures disclosed in Table 1, and the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

[0081] Benzopyrans that can serve as a Cox-2 selective inhibitor of the present invention include substituted benzopyran derivatives that are described in U.S. Patent Nos. 6,271,253 and 6,492,390. One such class of compounds is defined by the general formula shown below in formula **I**:



I

wherein X^1 is selected from O, S, $CR^c R^b$ and NR^a ;

wherein R^a is selected from hydrido, C_1 –C_3 –alkyl, (optionally substituted phenyl)-C_1 –C_3 –alkyl, acyl and carboxy-C_1 –C_6 –alkyl;

wherein each of R^b and R^c is independently selected from hydrido, C_1 –C_3 –alkyl, phenyl-C_1 –C_3 –alkyl, C_1 –C_3 –perfluoroalkyl, chloro, C_1 –C_6 –alkylthio, C_1 –C_6 –alkoxy, nitro, cyano and cyano-C_1 –C_3 –alkyl; or wherein $CR^b R^c$ forms a 3-6 membered cycloalkyl ring;

wherein R^1 is selected from carboxyl, aminocarbonyl, C_1 –C_6 –alkylsulfonylaminocarbonyl and C_1 –C_6 –alkoxycarbonyl;

wherein R^2 is selected from hydrido, phenyl, thienyl, C_1 –C_6 –alkyl and C_2 –C_6 –alkenyl;

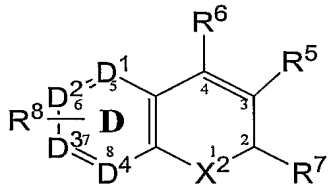
wherein R^3 is selected from C_1 –C_3 –perfluoroalkyl, chloro, C_1 –C_6 –alkylthio, C_1 –C_6 –alkoxy, nitro, cyano and cyano-C_1 –C_3 –alkyl;

wherein R^4 is one or more radicals independently selected from hydrido, halo, C_1 –C_6 –alkyl, C_2 –C_6 –alkenyl, C_2 –C_6 –alkynyl, halo-C_2 –C_6 –alkynyl, aryl-C_1 –C_3 –alkyl, aryl-C_2 –C_6 –alkynyl, aryl-C_2 –C_6 –alkenyl, C_1 –C_6 –alkoxy, methylenedioxy, C_1 –C_6 –alkylthio, C_1 –C_6 –alkylsulfinyl, aryloxy, arylthio, arylsulfinyl, heteroaryloxy, C_1 –C_6 –alkoxy-C_1 –C_6 –alkyl, aryl-C_1 –C_6 –alkyloxy, heteroaryl-C_1 –C_6 –alkyloxy, aryl-C_1 –C_6 –alkoxy-C_1 –C_6 –alkyl, C_1 –C_6 –haloalkyl, C_1 –C_6 –haloalkoxy, C_1 –C_6 –haloalkylthio, C_1 –C_6 –haloalkylsulfinyl, C_1 –C_6 –haloalkylsulfonyl, C_1 –C_3 –(haloalkyl-$_1$ –C_3 –hydroxyalkyl, C_1 –C_6 –hydroxyalkyl, hydroxyimino-C_1 –C_6 –alkyl, C_1 –C_6 –alkylamino, arylamino, aryl-C_1 –C_6 –alkylamino, heteroarylamino, heteroaryl-C_1 –C_6 –alkylamino, nitro, cyano, amino, aminosulfonyl, C_1 –C_6 –alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aryl-C_1 –C_6 –alkylaminosulfonyl, heteroaryl-C_1 –C_6 –alkylaminosulfonyl, heterocyclylsulfonyl, C_1 –C_6 –alkylsulfonyl, aryl-C_1 –C_6 –alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aryl-C_1 –C_6 –alkylcarbonyl, heteroaryl-C_1 –C_6 –alkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, C_1 –C_1 –alkoxycarbonyl, formyl, C_1 –C_6 –haloalkylcarbonyl and C_1 –C_6 –alkylcarbonyl; and

wherein the A ring atoms A^1, A^2, A^3 and A^4 are independently selected from carbon and nitrogen with the proviso that at least two of A^1, A^2, A^3 and A^4 are carbon;

or wherein R^4 together with ring A forms a radical selected from naphthyl, quinolyl, isoquinolyl, quinolizinyl, quinoxalinyl and dibenzofuryl, or an isomer or pharmaceutically acceptable salt thereof.

[0082] Another class of benzopyran derivatives that can serve as the Cox-2 selective inhibitor of the present invention includes compounds having the structure of formula **II**:



II

wherein X^2 is selected from O, S, $CR^c R^b$ and NR^a ;

wherein R^a is selected from hydrido, C_1 –C_3 –alkyl, (optionally substituted phenyl)-C_1 –C_3 –alkyl, alkylsulfonyl, phenylsulfonyl, benzylsulfonyl, acyl and carboxy-C_1 –C_6 –alkyl;

wherein each of R^b and R^c is independently selected from hydrido, C_1 –C_3 –alkyl, phenyl-C_1 –C_3 –alkyl, C_1 –C_3 –perfluoroalkyl, chloro, C_1 –C_6 –alkylthio, C_1 –C_6 –alkoxy, nitro, cyano and cyano-C_1 –C_3 –alkyl;

or wherein $CR^c R^b$ form a cyclopropyl ring;

wherein R^5 is selected from carboxyl, aminocarbonyl, C_1 –C_6 –alkylsulfonylaminocarbonyl and C_1 –C_6 –alkoxycarbonyl;

wherein R^6 is selected from hydrido, phenyl, thienyl, C_2 –C_6 –alkynyl and C_2 –C_6 –alkenyl;

wherein R^7 is selected from C_1 –C_3 –perfluoroalkyl, chloro, C_1 –C_6 –alkylthio, C_1 –C_6 –alkoxy, nitro, cyano and cyano-C_1 –C_3 –alkyl;

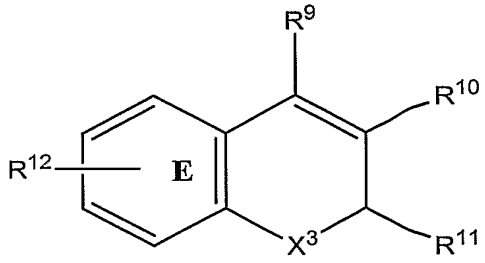
wherein R^8 is one or more radicals independently selected from hydrido, halo, C_1 –C_6 –alkyl, C_2 –C_6 –alkenyl, C_2 –C_6 –alkynyl, halo-C_2 –C_6 –alkynyl, aryl-C_1 –C_3 –alkyl, aryl-C_2 –C_6 –alkynyl, aryl-C_2 –C_6 –alkenyl, C_1 –C_6 –alkoxy, methylenedioxy, C_1 –C_6 –alkylthio, C_1 –C_6 –alkylsulfinyl, —

$O(CF_2)_2$ O—, aryloxy, arylthio, arylsulfinyl, heteroaryloxy, C_1 –C_6 –alkoxy-C_1 –C_6 –alkyl, aryl-C_1 –C_6 –alkyloxy, heteroaryl-C_1 –C_6 –alkyloxy, aryl-C_1 –C_6 –alkoxy-C_1 –C_6 –alkyl, C_1 –C_6 –haloalkyl, C_1 –C_6 –haloalkoxy, C_1 –C_6 –haloalkylthio, C_1 –C_6 –haloalkylsulfinyl, C_1 –C_6 –haloalkylsulfonyl, C_1 –C_3 –(haloalkyl-C_1 –C_3 –hydroxyalkyl), C_1 –C_6 –hydroxyalkyl, hydroxyimino-C_1 –C_6 –alkyl, C_1 –C_6 –alkylamino, arylamino, aryl-C_1 –C_6 –alkylamino, heteroarylamino, heteroaryl-C_1 –C_6 –alkylamino, nitro, cyano, amino, aminosulfonyl, C_1 –C_6 –alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aryl-C_1 –C_6 –alkylaminosulfonyl, heteroaryl-C_1 –C_6 –alkylaminosulfonyl, heterocyclylsulfonyl, C_1 –C_6 –alkylsulfonyl, aryl-C_1 –C_6 –alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aryl-C_1 –C_6 –alkylcarbonyl, heteroaryl-C_1 –C_6 –alkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, C_1 –C_6 –alkoxycarbonyl, formyl, C_1 –C_6 –haloalkylcarbonyl and C_1 –C_6 –alkylcarbonyl; and

wherein the D ring atoms D^1, D^2, D^3 and D^4 are independently selected from carbon and nitrogen with the proviso that at least two of D^1, D^2, D^3 and D^4 are carbon; or

wherein R^8 together with ring D forms a radical selected from naphthyl, quinolyl, isoquinolyl, quinolizinyl, quinoxalinyl and dibenzofuryl; or an isomer or pharmaceutically acceptable salt thereof.

[0083] Other benzopyran Cox-2 selective inhibitors useful in the practice of the present invention are described in U.S. Patent Nos. 6,034,256 and 6,077,850. The general formula for these compounds is shown in formula III:



III

wherein X^3 is selected from the group consisting of O or S or NR^a;

wherein R^a is alkyl;

wherein R^9 is selected from the group consisting of H and aryl;

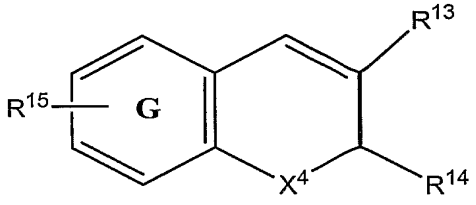
wherein R^{10} is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

wherein R^{11} is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

wherein R^{12} is selected from the group consisting of one or more radicals selected from H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or

wherein R^{12} together with ring E forms a naphthyl radical; or an isomer or pharmaceutically acceptable salt thereof; and including the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

[0084] A related class of compounds useful as Cox-2 selective inhibitors in the present invention is described by Formulas **IV** and **V** below:



IV

wherein X^4 is selected from O or S or NR^a ;

wherein R^a is alkyl;

wherein R^{13} is selected from carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

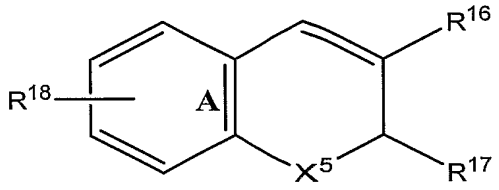
wherein R^{14} is selected from haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

wherein R^{15} is one or more radicals selected from hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl;

or wherein R^{15} together with ring G forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[0085] Formula **V** is:



V

wherein:

X^5 is selected from the group consisting of O or S or NR^b;

R^b is alkyl;

R^{16} is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

R^{17} is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein haloalkyl, alkyl, aralkyl, cycloalkyl, and aryl each is independently optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[0086] The Cox-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

R^{17} is selected from the group consisting of lower haloalkyl, lower cycloalkyl and phenyl; and

R^{18} is one or more radicals selected from the group of consisting of hydrido, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl; or

wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[0087] The Cox-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is carboxyl;

R^{17} is lower haloalkyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkyl, lower haloalkoxy, lower alkylamino, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, lower alkylsulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl; or wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[0088] The Cox-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

R^{17} is selected from the group consisting of fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl, and trifluoromethyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl, isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropyloxy, tertbutyloxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-(2-methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl and phenyl; or

wherein R^2 together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[0089] The Cox-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

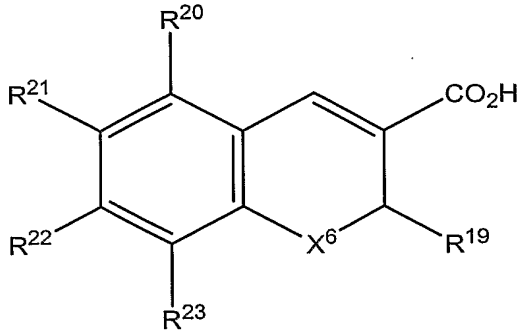
R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

R^{17} is selected from the group consisting trifluoromethyl and pentafluoroethyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, N,N-dimethylaminosulfonyl, N-methylaminosulfonyl, N-(2,2-dimethylethyl)aminosulfonyl, dimethylaminosulfonyl, 2-methylpropylaminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, and phenyl; or wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or prodrug thereof.

[0090] The Cox-2 selective inhibitor of the present invention can also be a compound having the structure of Formula **VI**:



VI

wherein:

X^6 is selected from the group consisting of O and S;

R^{19} is lower haloalkyl;

R^{20} is selected from the group consisting of hydrido, and halo;

R^{21} is selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower

dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, and 6- membered nitrogen-containing heterocyclosulfonyl;

R^{22} is selected from the group consisting of hydrido, lower alkyl, halo, lower alkoxy, and aryl; and

R^{23} is selected from the group consisting of the group consisting of hydrido, halo, lower alkyl, lower alkoxy, and aryl;

or an isomer or prodrug thereof.

[0091] The Cox-2 selective inhibitor can also be a compound of having the structure of Formula VI, wherein:

X^6 is selected from the group consisting of O and S;

R^{19} is selected from the group consisting of trifluoromethyl and pentafluoroethyl;

R^{20} is selected from the group consisting of hydrido, chloro, and fluoro;

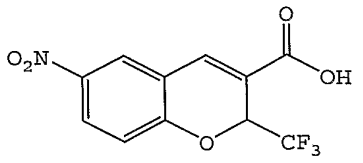
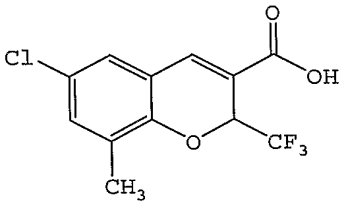
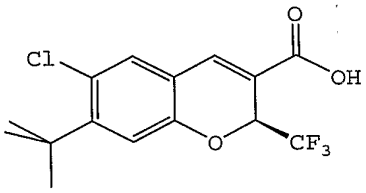
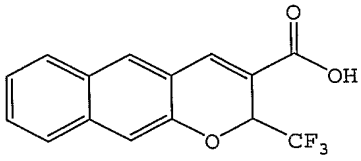
R^{21} is selected from the group consisting of hydrido, chloro, bromo, fluoro, iodo, methyl, tert-butyl, trifluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl, benzylaminosulfonyl, phenylethylaminosulfonyl, methylpropylaminosulfonyl, methylsulfonyl, and morpholinosulfonyl;

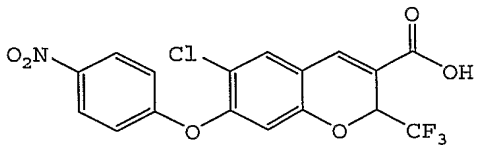
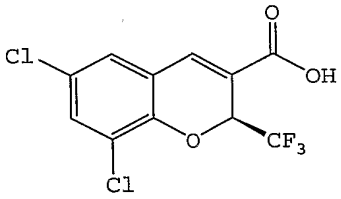
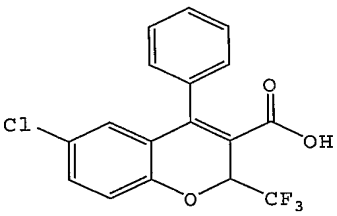
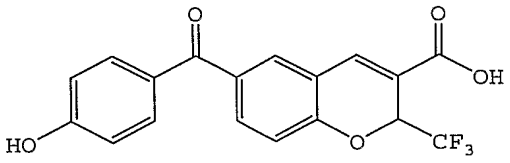
R^{22} is selected from the group consisting of hydrido, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, and phenyl; and

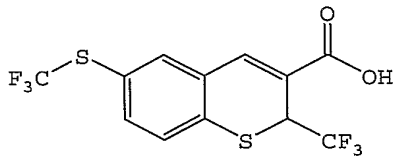
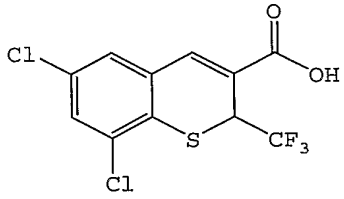
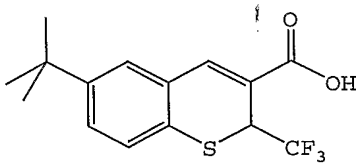
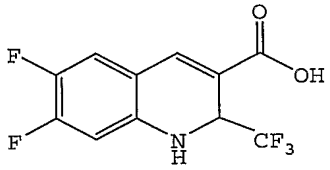
R^{23} is selected from the group consisting of hydrido, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, and phenyl;

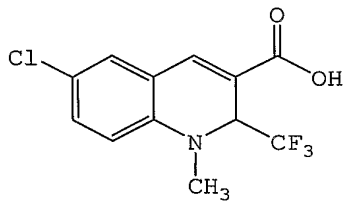
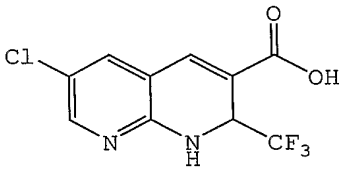
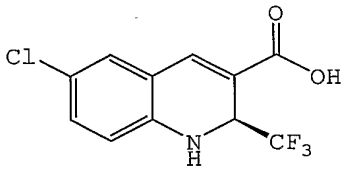
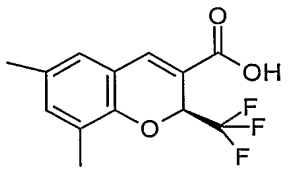
or an isomer or prodrug thereof.

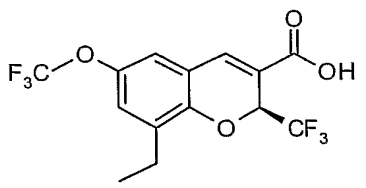
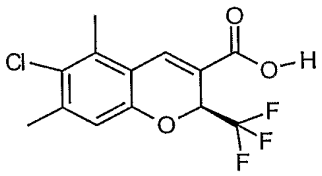
Table 1. Examples of Chromene Cox-2 Selective Inhibitors

Compound Number	Structural Formula
B-3	 6-Nitro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid
B-4	 6-Chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid
B-5	 ((S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl-2H–1-benzopyran-3-carboxylic acid
B-6	 2-Trifluoromethyl-2H-naphtho[2,3-b]pyran-3-carboxylic acid

Compound Number	Structural Formula
B-7	 6-Chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-8	 ((S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-9	 6-Chloro-2-(trifluoromethyl)-4-phenyl-2H-1-benzopyran-3-carboxylic acid
B-10	 6-(4-Hydroxybenzoyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid

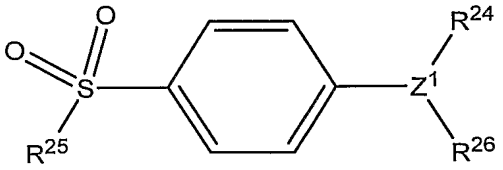
Compound Number	Structural Formula
B-11	 2-(Trifluoromethyl)-6-[(trifluoromethyl)thio]-2H-1-benzothiopyran-3-carboxylic acid
B-12	 6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid
B-13	 6-(1,1-Dimethylethyl)-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid
B-14	 6,7-Difluoro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid

Compound Number	Structural Formula
B-15	 6-Chloro-1,2-dihydro-1-methyl-2-(trifluoromethyl)-3-quinolinecarboxylic acid
B-16	 6-Chloro-2-(trifluoromethyl)-1,2-dihydro[1,8]naphthyridine-3-carboxylic acid
B-17	 ((S)-6-Chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid
B-18	 (2S)-6,8-dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid

Compound Number	Structural Formula
B-19	 (2S)-8-ethyl-6-(trifluoromethoxy)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid
B-20	 (2S)-6-chloro-5,7-dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid

[0092] In preferred embodiments the chromene Cox-2 inhibitor is selected from (S)-6-chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, (2S)-6,8-dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, (2S)-6-chloro-8-methyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, (2S)-8-ethyl-6-(trifluoromethoxy)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, (2S)-6-chloro-5,7-dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, and mixtures thereof.

[0093] In a preferred embodiment of the invention the Cox-2 inhibitor can be selected from the class of tricyclic Cox-2 selective inhibitors represented by the general structure of formula **VII**:



VII

wherein:

Z^1 is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

R^{24} is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R^{24} is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

R^{25} is selected from the group consisting of methyl or amino; and

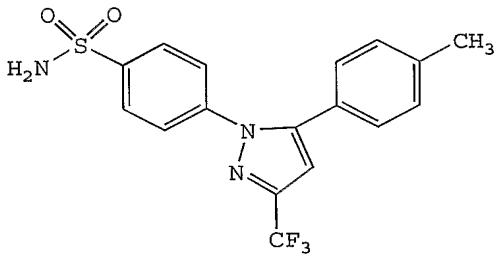
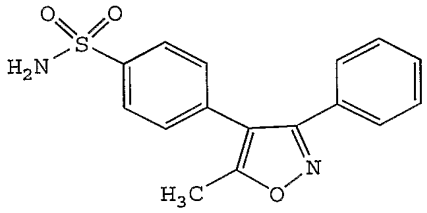
R^{26} is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl;

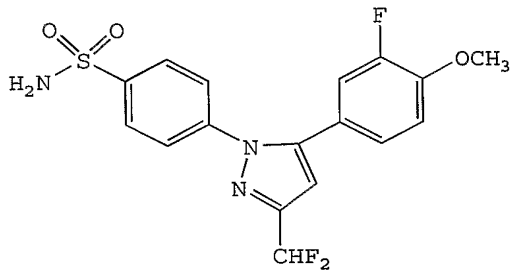
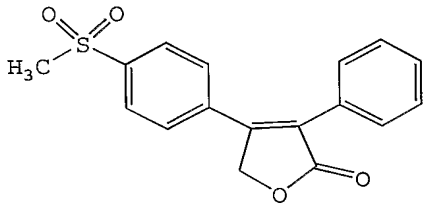
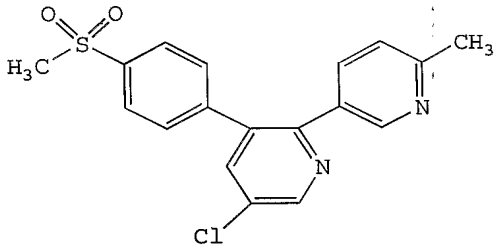
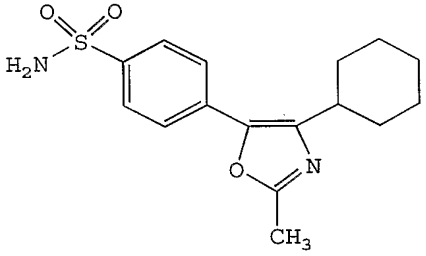
or a prodrug thereof.

[0094] In a preferred embodiment of the invention the tricyclic Cox-2 selective inhibitor represented by the above Formula VII is selected from the group of compounds, illustrated in Table 2, which includes celecoxib (B-21), valdecoxib (B-22), deracoxib (B-23), rofecoxib (B-24), etoricoxib (MK-663; B-25), JTE-522 (B-26), or prodrugs thereof.

[0095] Additional information about selected examples of the tricyclic Cox-2 selective inhibitors discussed above can be found as follows: celecoxib (CAS RN 169590-42-5, C-2779, SC-58653, and in U.S. Patent No. 5,466,823); deracoxib (CAS RN 169590-41-4); rofecoxib (CAS RN 162011-90-7); compound B-24 (U.S. Patent No. 5,840,924); compound B-26 (WO 00/25779); and etoricoxib (CAS RN 202409-33-4, MK-663, SC-86218, and in WO 98/03484).

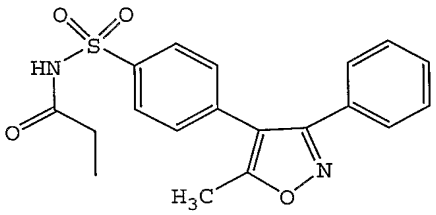
[0096] Table 2. Examples of Tricyclic Cox-2 Selective Inhibitors

Compound Number	**Structural Formula**
B-21	
B-22	

Compound Number	Structural Formula
B-23	
B-24	
B-25	
B-26	

[0097] In a more preferred embodiment of the invention, the Cox-2 selective inhibitor is selected from the group consisting of celecoxib, rofecoxib and etoricoxib.

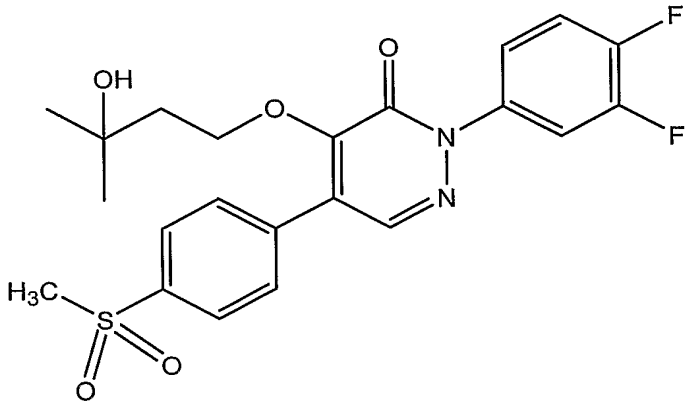
[0098] In a preferred embodiment, parecoxib (See, U.S. Patent No. 5,932,598), having the structure shown in B-27, and which is a therapeutically effective prodrug of the tricyclic Cox-2 selective inhibitor valdecoxib, B-22, (See, U.S. Patent No. 5,633,272), may be advantageously employed as the Cox-2 inhibitor of the present invention.



B-27

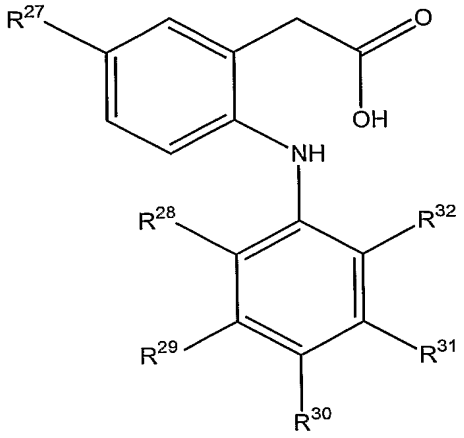
[0100] A preferred form of parecoxib is sodium parecoxib.

[0101] Another tricyclic Cox-2 selective inhibitor useful in the present invention is the compound ABT-963, having the formula B-28 shown below, that has been previously described in International Publication Number WO 00/24719.



B-28

[0102] In a further embodiment of the invention, the Cox-2 inhibitor can be selected from the class of phenylacetic acid derivative Cox-2 selective inhibitors represented by the general structure of formula **VIII**:



VIII

wherein:

R^{27} is methyl, ethyl, or propyl;

R^{28} is chloro or fluoro;

R^{29} is hydrogen, fluoro, or methyl;

R^{30} is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxyl;

R^{31} is hydrogen, fluoro, or methyl; and

R^{32} is chloro, fluoro, trifluoromethyl, methyl, or ethyl,

provided that R^{28}, R^{29}, R^{30} and R^{31} are not all fluoro when R^{27} is ethyl and R^{30} is H.

[0103] An exemplary phenylacetic acid derivative Cox-2 selective inhibitor that is described in WO 99/11605 is a compound that has the structure shown in formula **VIII**,

wherein:

R^{27} is ethyl;

R^{28} and R^{30} are chloro;

R^{29} and R^{31} are hydrogen; and

R^{32} is methyl.

[0104] Another phenylacetic acid derivative Cox-2 selective inhibitor is a compound that has the structure shown in formula **VIII**,

wherein:

R^{27} is propyl;

R^{28} and R^{30} are chloro;

R^{29} and R^{31} are methyl; and

R^{32} is ethyl.

[0105] Another phenylacetic acid derivative Cox-2 selective inhibitor that is disclosed in WO 02/20090 is a compound that is referred to as COX-189 (also termed lumiracoxib; CAS Reg. No. 220991-20-8), having the structure shown in formula **VIII**,

wherein:

R^{27} is methyl;

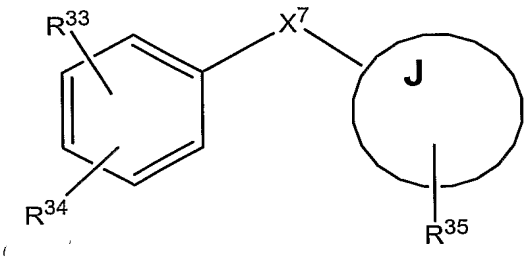
R^{28} is fluoro;

R^{32} is chloro; and

R^{29}, R^{30}, and R^{31} are hydrogen.

[0106] Compounds having a structure similar to that shown in formula **VIII**, that can serve as the Cox-2 selective inhibitor of the present invention, are described in U.S. Patent Nos. 6,451,858, 6,310,099, 6,291,523, and 5,958,978.

[0107] Other Cox-2 selective inhibitors that can be used in the present invention have the general structure shown in formula **IX**, where the J group is a carbocycle or a heterocycle. Preferred embodiments have the structure:



IX

wherein:

X^7 is O; J is 1-phenyl; R^{33} is 2-$NHSO_2CH_3$; R^{34} is 4-NO_2; and there is no R^{35} group, (nimesulide), or

X^7 is O; J is 1-oxo-inden-5-yl; R^{33} is 2-F; R^{34} is 4-F; and R^{35} is 6-$NHSO_2CH_3$, (flosulide); or

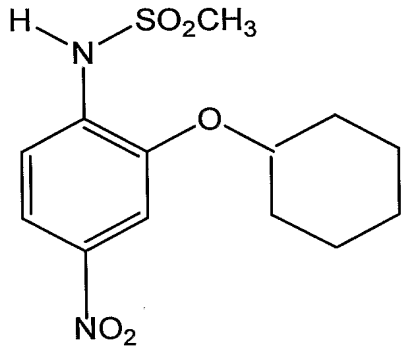
X^7 is O; J is cyclohexyl; R^{33} is 2-$NHSO_2CH_3$; R^{34} is 5-NO_2; and there is no R^{35} group, (NS-398); or

X^7 is S; J is 1-oxo-inden-5-yl; R^{33} is 2-F; R^{34} is 4-F; and R^{35} is 6-$N^-SO_2CH_3 \cdot Na^+$, (L-745337); or

X^7 is S; J is thiophen-2-yl; R^{33} is 4-F; there is no R^{34} group; and R^{35} is 5-$NHSO_2CH_3$, (RWJ-63556); or

X^7 is O; J is 2-oxo-5(R)-methyl-5-(2,2,2-trifluoroethyl)furan-(5H)-3-yl; R^{33} is 3-F; R^{34} is 4-F; and R^{35} is 4-(p-SO_2CH_3)C_6H_4, (L-784512).

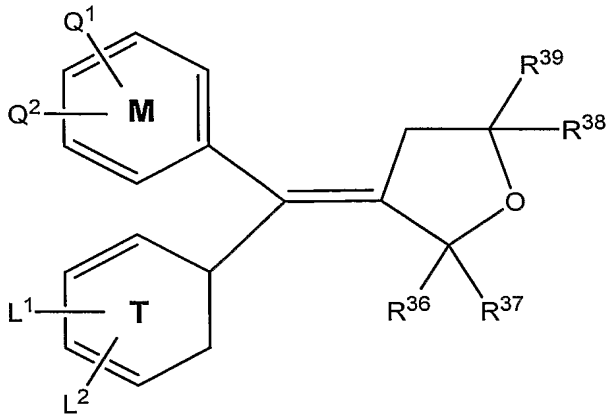
[0108] The Cox-2 selective inhibitor NS-398, also known as N-(2-cyclohexyloxynitrophenyl) methane sulfonamide (CAS RN 123653-11-2), having a structure as shown below in formula B-29, has been described in, for example, Yoshimi, N. *et al.,* in *Japanese J. Cancer Res., 90(4):*406 – 412 (1999).



B-29

[0109] An evaluation of the anti-inflammatory activity of the Cox-2 selective inhibitor, RWJ 63556, in a canine model of inflammation, was described by Kirchner *et al.,* in *J Pharmacol Exp Ther 282*, 1094-1101 (1997).

[0110] Materials that can serve as the Cox-2 selective inhibitor of the present invention include diarylmethylidenefuran derivatives that are described in U.S. Patent No. 6,180,651. Such diarylmethylidenefuran derivatives have the general formula shown below in formula **X**:



X

wherein:

the rings T and M independently are a phenyl radical, a naphthyl radical, a radical derived from a heterocycle comprising 5 to 6 members and possessing from 1 to 4 heteroatoms, or a radical derived from a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

at least one of the substituents Q^1, Q^2, L^1 or L^2 is an —$S(O)_n$ —R group, in which n is an integer equal to 0, 1 or 2 and R is a lower alkyl radical having 1 to 6 carbon atoms, a lower haloalkyl radical having 1 to 6 carbon atoms, or an $-SO_2NH_2$ group;

and is located in the para position,

the others independently being a hydrogen atom, a halogen atom, a lower alkyl radical having 1 to 6 carbon atoms, a trifluoromethyl radical, or a lower O-alkyl radical having 1 to 6 carbon atoms, or Q^1 and Q^2 or L^1 and L^2 are a methylenedioxy group; and

R^{36}, R^{37}, R^{38} and R^{39} independently are a hydrogen atom, a halogen atom, a lower alkyl radical having 1 to 6 carbon atoms, a lower haloalkyl radical having 1 to 6 carbon atoms, or an aromatic radical selected from the group consisting of phenyl, naphthyl, thienyl, furyl and pyridyl; or,

R^{36}, R^{37} or R^{38}, R^{39} are an oxygen atom; or

R^{36}, R^{37} or R^{38}, R^{39}, together with the carbon atom to which they are attached, form a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

or an isomer or prodrug thereof.

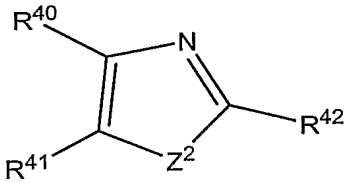
[0111] Particular diarylmethylidenefuran derivatives that can serve as the Cox-2 selective inhibitor of the present invention include, for example, N-(2-cyclohexyloxynitrophenyl)methane sulfonamide, and (E)-4-[(4-methylphenyl)(tetrahydro-2-oxo-3-furanylidene) methyl]benzenesulfonamide.

[0112] Other Cox-2 selective inhibitors that are useful in the present invention include darbufelone (Pfizer), CS-502 (Sankyo), LAS 34475 (Almirall Profesfarma), LAS 34555 (Almirall Profesfarma), S-33516 (Servier), SD 8381 (Pharmacia, described in U.S. Patent No. 6,034,256), BMS-347070 (Bristol Myers Squibb, described in U.S. Patent No. 6,180,651), MK-966 (Merck), L-783003 (Merck), T-614 (Toyama), D-1367 (Chiroscience), L-748731 (Merck), CT3 (Atlantic Pharmaceutical), CGP-28238 (Novartis), BF-389 (Biofor/Scherer), GR-253035 (Glaxo Wellcome), 6-dioxo-9H-purin-8-yl-cinnamic acid (Glaxo Wellcome), and S-2474 (Shionogi).

[0113] Compounds that may act as Cox-2 selective inhibitors of the present invention include multibinding compounds containing from 2 to 10 ligands covanlently attached to one or more linkers, as described in U.S. Patent No. 6,395,724.

[0114] Conjugated linoleic, as described in U.S. Patent No. 6,077,868, is useful as a Cox-2 selective inhibitor in the present invention.

[0115] Compounds that can serve as a Cox-2 selective inhibitor of the present invention include heterocyclic aromatic oxazole compounds that are described in U.S. Patents 5,994,381 and 6,362,209. Such heterocyclic aromatic oxazole compounds have the formula shown below in formula **XI**:

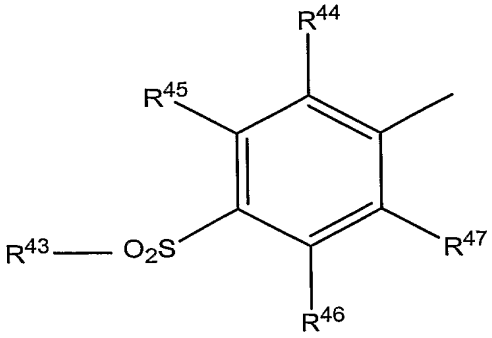


XI

wherein:

Z^2 is an oxygen atom;

one of R^{40} and R^{41} is a group of the formula



wherein:

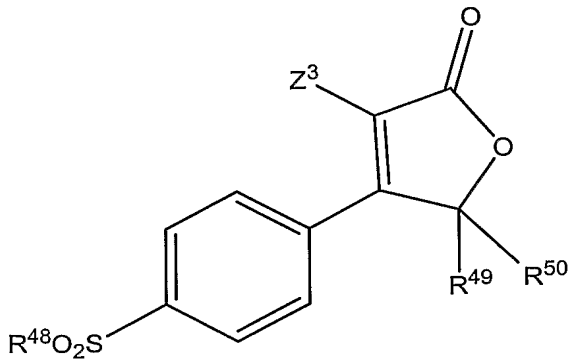
R^{43} is lower alkyl, amino or lower alkylamino; and

R^{44}, R^{45}, R^{46} and R^{47} are the same or different and each is hydrogen atom, halogen atom, lower alkyl, lower alkoxy, trifluoromethyl, hydroxyl or amino, provided that at least one of R^{44}, R^{45}, R^{46} and R^{47} is not hydrogen atom, and the other is an optionally substituted cycloalkyl, an optionally substituted heterocyclic group or an optionally substituted aryl; and

R^{30} is a lower alkyl or a halogenated lower alkyl,

and a pharmaceutically acceptable salt thereof.

[0116] Cox-2 selective inhibitors that are useful in the method and compositions of the present invention include compounds that are described in U.S. Patent Nos. 6,080,876 and 6,133,292, and described by formula **XII**:



XII

wherein:

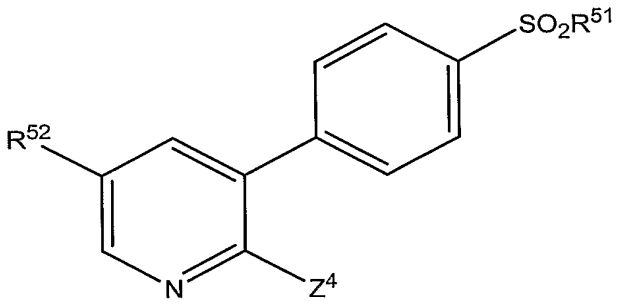
Z^3 is selected from the group consisting of linear or branched C_1 – C_6 alkyl, linear or branched C_1 –C_6 alkoxy, unsubstituted, mono-, di- or tri-substituted phenyl or naphthyl wherein the substituents are selected from the group consisting of hydrogen, halo, C_1 –C_3 alkoxy, CN, C_1 –C_3 fluoroalkyl C_1 –C_3 alkyl, and –CO_2 H;

R^{48} is selected from the group consisting of NH_2 and CH_3,

R^{49} is selected from the group consisting of C_1 –C_6 alkyl unsubstituted or substituted with C_3 –C_6 cycloalkyl, and C_3 –C_6 cycloalkyl;

R^{50} is selected from the group consisting of C_1 –C_6 alkyl unsubstituted or substituted with one, two or three fluoro atoms, and C_3 – C_6 cycloalkyl; with the proviso that R^{49} and R^{50} are not the same.

[0117] Pyridines that are described in U.S. Patent Nos. 6,596,736, 6,369,275, 6,127,545, 6,130,334, 6,204,387, 6,071,936, 6,001,843 and 6,040,450, and can seve as Cox-2 selective inhibitors of the present invention, have the general formula described by formula **XIII**:



XIII

wherein:

R^{51} is selected from the group consisting of CH_3, NH_2, $NHC(O)CF_3$, and $NHCH_3$;

Z^4 is a mono-, di-, or trisubstituted phenyl or pyridinyl (or the N-oxide thereof), wherein the substituents are selected from the group consisting of hydrogen, halo, C_1 –C_6 alkoxy, C_1 –C_6 alkylthio, CN, C_1 –C_6 alkyl, C_1 –C_6 fluoroalkyl, N_3, –CO_2R^{53}, hydroxyl, –$C(R^{54})(R^{55})$—OH, – C_1 – C_6 alkyl-CO_2—R^{56}, C_1 –C_6 fluoroalkoxy;

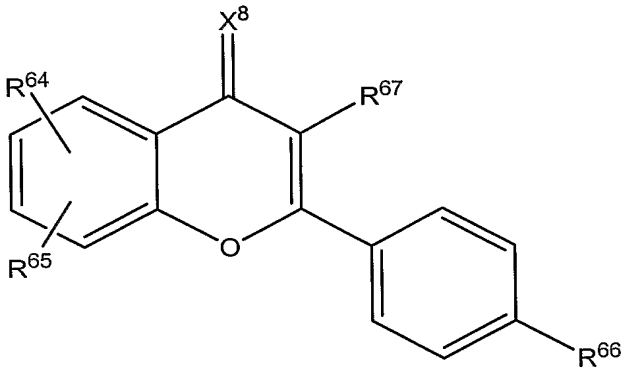
R^{52} is selected from the group consisting of halo, C_1 –C_6 alkoxy, C_1 –C_6 alkylthio, CN, C_1 –C_6 alkyl, C_1 –C_6 fluoroalkyl, N_3, —CO_2R^{57}, hydroxyl,

—C(R^{58})(R^{59})—OH, — C_1 –C_6 alkyl-CO_2—R^{60}, C_1 –C_6 fluoroalkoxy, NO_2, $NR^{61}R^{62}$, and $NHCOR^{63}$;

R^{53}, R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, R^{61}, R^{62}, and R^{63}, are each independently selected from the group consisting of hydrogen andC_1 –C_6 alkyl;

or R^{54} and R^{55}, R^{58} and R^{59}, or R^{61} and R^{62} together with the atom to which they are attached form a saturated monocyclic ring of 3, 4, 5, 6, or 7 atoms.

[0118] Materials that can serve as the Cox-2 selective inhibitor of the present invention include diarylbenzopyran derivatives that are described in U.S. Patent No. 6,340,694. Such diarylbenzopyran derivatives have the general formula shown below in formula **XIV**:



XIV

wherein:

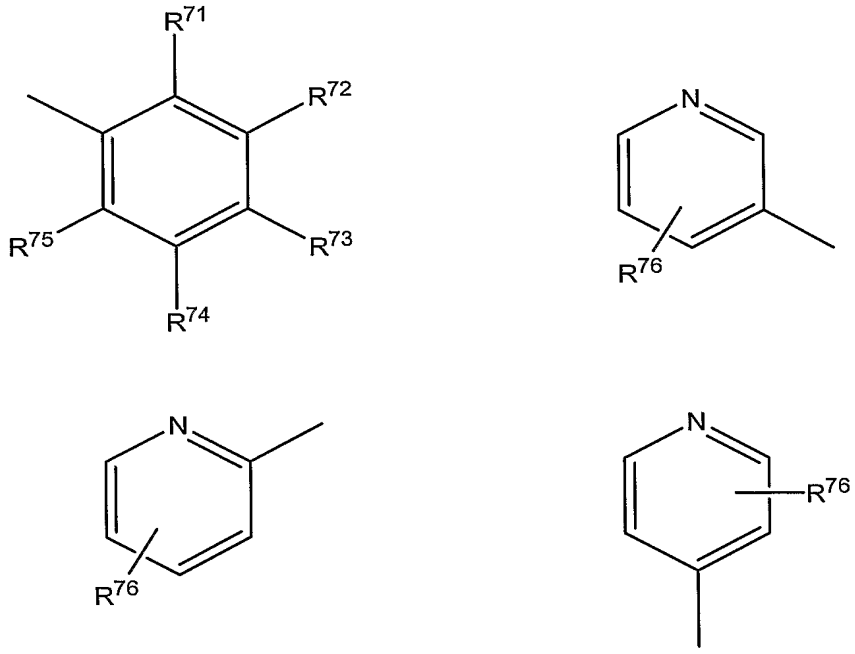
X^8 is an oxygen atom or a sulfur atom;

R^{64} and R^{65}, identical to or different from each other, are independently a hydrogen atom, a halogen atom, a C_1 –C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxyl group, a nitro group, a nitrile group, or a carboxyl group;

R^{66} is a group of a formula: $S(O)_nR^{68}$ wherein n is an integer of 0~2, R^{68} is a hydrogen atom, a C_1 –C_6 lower alkyl group, or a group of a formula: NR^{69} R^{70} wherein R^{69} and R^{70}, identical to or different from each other, are independently a hydrogen atom, or a C_1 –C_6 lower alkyl group; and

R^{67} is oxazolyl, benzo[b]thienyl, furanyl, thienyl, naphthyl, thiazolyl, indolyl, pyrolyl, benzofuranyl, pyrazolyl, pyrazolyl substituted with a C_1 –C_6 lower

alkyl group, indanyl, pyrazinyl, or a substituted group represented by the following structures:



wherein:

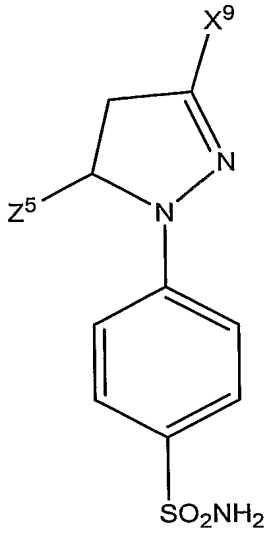
R^{71} through R^{75}, identical to or different from one another, are independently a hydrogen atom, a halogen atom, a C_1 –C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxyl group, a hydroxyalkyl group, a nitro group, a group of a formula: $S(O)_nR^{68}$, a group of a formula: NR^{69} R^{70}, a trifluoromethoxy group, a nitrile group a carboxyl group, an acetyl group, or a formyl group,

wherein n, R^{68}, R^{69} and R^{70} have the same meaning as defined by R^{66} above; and

R^{76} is a hydrogen atom, a halogen atom, a C_1 –C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxyl group, a trifluoromethoxy group, a carboxyl group, or an acetyl group.

[0119] Materials that can serve as the Cox-2 selective inhibitor of the present invention include 1-(4-sulfamylaryl)-3-substituted-5-aryl-2-pyrazolines that are described in U.S. Patent No. 6,376,519. Such 1-(4-

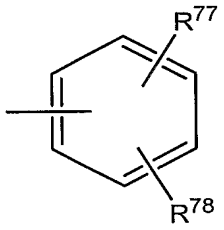
sulfamylaryl)-3-substituted-5-aryl-2-pyrazolines have the formula shown below in formula **XV**:



XV

wherein:

X^9 is selected from the group consisting of C_1 –C_6 trihalomethyl, preferably trifluoromethyl; C_1 –C_6 alkyl; and an optionally substituted or di-substituted phenyl group of formula **XVI**:



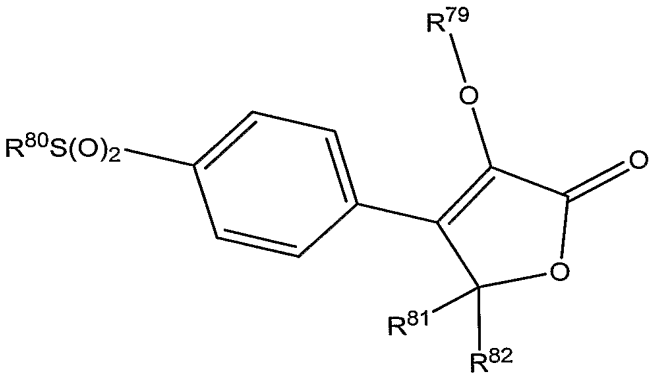
XVI

wherein:

R^{77} and R^{78} are independently selected from the group consisting of hydrogen, halogen, preferably chlorine, fluorine and bromine; hydroxyl; nitro; C_1 –C_6 alkyl, preferably C_1 –C_3 alkyl; C_1 –C_6 alkoxy, preferably C_1 – C_3 alkoxy; carboxy; C_1 –C_6 trihaloalkyl, preferably trihalomethyl, most preferably trifluoromethyl; and cyano;

Z^5 is selected from the group consisting of substituted and unsubstituted aryl.

[0120] Compounds useful as Cox-2 selective inhibitors of the present invention include heterocycles that are described in U.S. Patent No. 6,153,787. Such heterocycles have the general formulas shown below in formulas **XVII** and **XVIII**:



XVII

wherein:

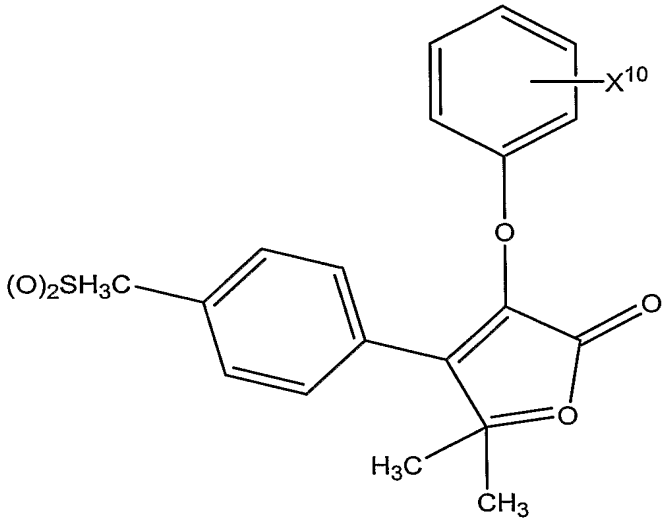
R^{79} is a mono-, di-, or tri-substituted C_1 –C_{12} alkyl, or a mono-, or an unsubstituted or mono-, di- or tri-substituted linear or branched C_2 –C_{10} alkenyl, or an unsubstituted or mono-, di- or tri-substituted linear or branched C_2 –C_{10} alkynyl, or an unsubstituted or mono-, di- or tri-substituted C_3 –C_{12} cycloalkenyl, or an unsubstituted or mono-, di- or tri-substituted C_5 –C_{12} cycloalkynyl, wherein the substituents are selected from the group consisting of halo selected from F, Cl, Br, and I, OH, CF_3, C_3 –C_6 cycloalkyl, =O,dioxolane, CN;

R^{80} is selected from the group consisting of CH_3, NH_2, $NHC(O)CF_3$, and $NHCH_3$;

R^{81} and R^{82} are independently selected from the group consisting of hydrogen and C_1 –C_{10} alkyl; or

R^{81} and R^{82} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms.

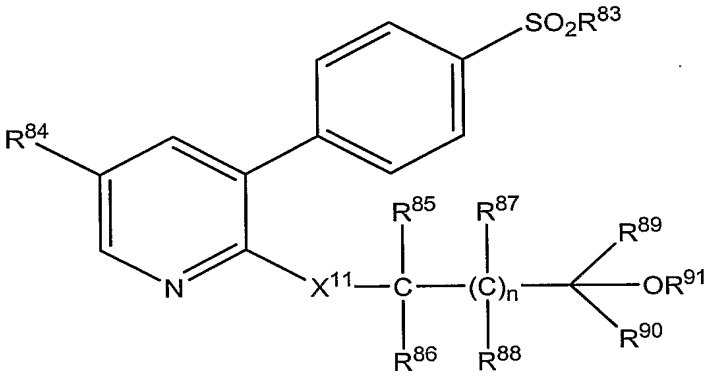
[0121] Formula **XVIII** is:



XVIII

wherein X^{10} is fluoro or chloro.

[0122] Materials that can serve as the Cox-2 selective inhibitor of the present invention include 2,3,5-trisubstituted pyridines that are described in U.S. Patent No. 6,046,217. Such pyridines have the general formula shown below in formula **XIX**:



XIX

or a pharmaceutically acceptable salt thereof,

wherein:

X^{11} is selected from the group consisting of O, S, and a bond;

n is 0 or 1;

R^{83} is selected from the group consisting of CH_3, NH_2, and $NHC(O)CF_3$;

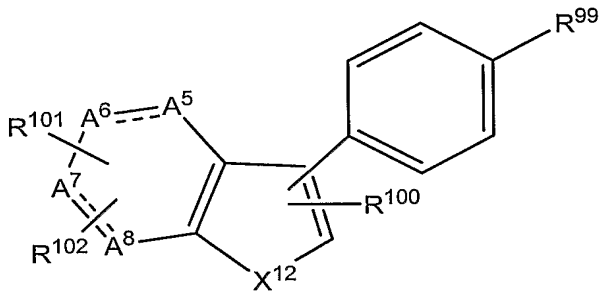
R^{84} is selected from the group consisting of halo, C_1 –C_6 alkoxy, C_1 –C_6 alkylthio, CN, C_1 –C_6 alkyl, C_1 –C_6 fluoroalkyl, N_3, —CO_2 R^{92},

hydroxyl, —C(R^{93})(R^{94})—OH, —C_1 –C_6 alkyl-CO_2 —R^{95}, C_1 –C_6 fluoroalkoxy, NO_2, NR^{96} R^{97}, and $NHCOR^{98}$;

R^{85} to R^{89} are independently selected from the group consisting of hydrogen and C_1 –C_6 alkyl; or

R^{85} and R^{89}, or R^{89} and R^{90} together with the atoms to which they are attached form a carbocyclic ring of 3, 4, 5, 6 or 7 atoms, or R^{85} and R^{87} are joined to form a bond.

[0123] Compounds that are useful as the Cox-2 selective inhibitor of the present invention include diaryl bicyclic heterocycles that are described in U.S. Patent No. 6,329,421. Such diaryl bicyclic heterocycles have the general formula shown below in formula **XX**:



XX

and pharmaceutically acceptable salts thereof wherein:

—A^5=A^6—A^7=A^8— is selected from the group consisting of

(a) —CH=CH—CH=CH—,

(b) —CH_2 —CH_2 —CH_2 —C(O)—, —CH_2 —CH_2 —C(O)—CH_2 —, —CH_2 —C(O)—CH_2 —CH_2, —C(O)—CH_2 —CH_2 —CH_2,

(c) —CH_2 —CH_2 —C(O)—, —CH_2 —C(O)—CH_2 —, —C(O)—CH_2 —CH_2 —

(d) —CH_2 —CH_2 —O—C(O)—, CH_2 —O—C(O)—CH_2 —, —O—C(O)—CH_2 —CH_2 —,

(e) —CH_2 —CH_2 —C(O)—O—, —CH_2 —C(O)—OCH_2 —, —C(O)—O—CH_2 —CH_2 —,

(f) —C(R^{105})$_2$ —O—C(O)—, —C(O)—O—C(R^{105})$_2$ —, —O—C(O)—C(R^{105})$_2$ —, —C(R^{105})$_2$ —C(O)—O—,

(g) —N=CH—CH=CH—,

(h) —CH=N—CH=CH—,
(i) —CH=CH—N=CH—,
(j) —CH=CH—CH=N—,
(k) —N=CH—CH=N—,
(l) —N=CH—N=CH—,
(m) —CH=N—CH=N—,
(n) —S—CH=N—,
(o) —S—N=CH—,
(p) —N=N—NH—,
(q) —CH=N—S—, and
(r) —N=CH—S—;

R^{99} is selected from the group consisting of $S(O)_2CH_3$, $S(O)_2NH_2$, $S(O)_2NHCOCF_3$, $S(O)(NH)CH_3$, $S(O)(NH)NH_2$, $S(O)(NH)NHCOCF_3$, $P(O)(CH_3)OH$, and $P(O)(CH_3)NH_2$;

R^{100} is selected from the group consisting of

(a) C_1 –C_6 alkyl,
(b) C_3 –C_7 cycloalkyl,
(c) mono- or di-substituted phenyl or naphthyl wherein the substituent is selected from the group consisting of
    (1) hydrogen,
    (2) halo, including F, Cl, Br, I,
    (3) C_1 –C_6 alkoxy,
    (4) C_1 –C_6 alkylthio,
    (5) CN,
    (6) CF_3,
    (7) C_1 –C_6 alkyl,
    (8) N_3,
    (9) —CO_2 H,
    (10) —CO_2 —C_1 –C_4 alkyl,
    (11) —C(R^{103})(R^{104})—OH,
    (12) —C(R^{103})(R^{104})—O—C_1 –C_4 alkyl, and
    (13) —C_1 –C_6 alkyl-CO_2 —R^{106};

(d) mono- or di-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additional N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said substituents are selected from the group consisting of

(1) hydrogen,

(2) halo, including fluoro, chloro, bromo and iodo,

(3) C_1 –C_6 alkyl,

(4) C_1 –C_6 alkoxy,

(5) C_1 –C_6 alkylthio,

(6) CN,

(7) CF_3,

(8) N_3,

(9) —$C(R^{103})(R^{104})$—OH, and

(10) —$C(R^{103})(R^{104})$—O—C_1 –C_4 alkyl;

(e) benzoheteroaryl which includes the benzo fused analogs of (d);

R^{101} and R^{102} are the substituents residing on any position of –A^5=A^6—A^7=A^8— and are selected independently from the group consisting of

(a) hydrogen,

(b) CF_3,

(c) CN,

(d) C_1 –C_6 alkyl,

(e) —Q^3 wherein Q^3 is Q^4, CO_2 H, $C(R^{103})(R^{104})$OH,

(f) —O—Q^4,

(g) —S—Q^4, and

(h) optionally substituted:

(1) —C_1 –C_5 alkyl-Q^3,

(2) —O—C_1 –C_5 alkyl-Q^3,

(3) —S—C_1 –C_5 alkyl-Q^3,

(4) —C_1 –C_3 alkyl-O—C_{1-3} alkyl-Q^3,

(5) —C_1 –C_3 alkyl-S—C_{1-3} alkyl-Q^3,

(6) —C_1 –C_5 alkyl-O—Q^4,

(7) —C_1 –C_5 alkyl-S—Q^4,

wherein the substituent resides on the alkyl chain and the substituent is C_1 –C_3 alkyl, and Q^3 is Q^4, CO_2 H, $C(R^{103})(R^{104})OH$ Q^4 is CO_2 —C_1 –C_4 alkyl, tetrazolyl-5-yl, or $C(R^{103})(R^{104})O$—C_1 –C_4 alkyl;

R^{103}, R^{104} and R^{105} are each independently selected from the group consisting of hydrogen and C_1 –C_6 alkyl; or

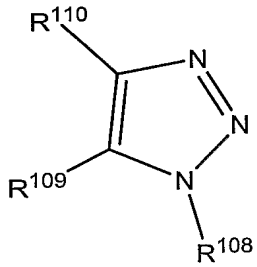
R^{103} and R^{104} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms, or two R^{105} groups on the same carbon form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

R^{106} is hydrogen or C_1 –C_6 alkyl;

R^{107} is hydrogen, C_1 —C_6 alkyl or aryl;

X^7 is O, S, NR^{107}, CO, $C(R^{107})_2$, $C(R^{107})(OH)$, —$C(R^{107})$=$C(R^{107})$—; —$C(R^{107})$=N—; or —N=$C(R^{107})$—.

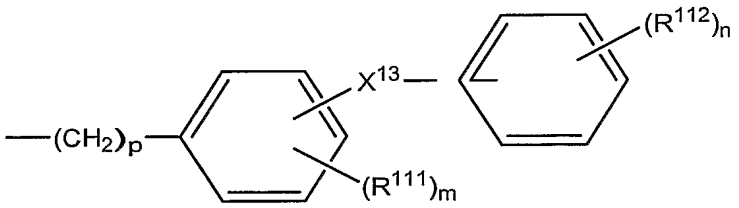
[0124] Compounds that may act as Cox-2 selective inhibitors include salts of 5-amino or a substituted amino 1,2,3-triazole compound that are described in U.S. Patent No. 6,239,137. The salts are of a class of compounds of formula **XXI**:



XXI

wherein:

R^{108} is:



wherein:

p is 0 to 2; m is 0 to 4; and n is 0 to 5;

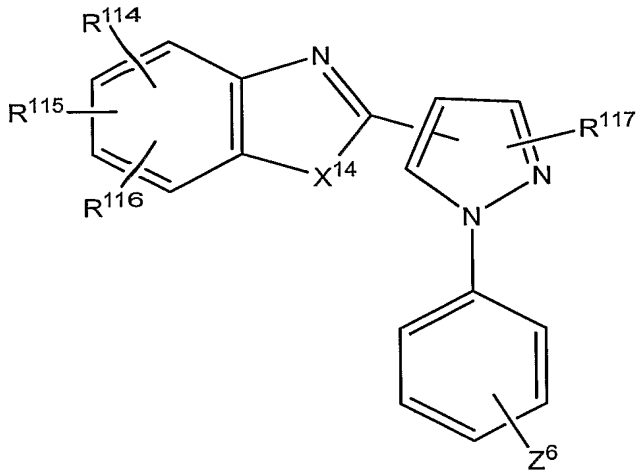
X^{13} is O, S, SO, SO_2, CO, CHCN, CH_2 or $C=NR^{113}$ where R^{113} is hydrogen, loweralkyl, hydroxyl, loweralkoxy, amino, loweralkylamino, diloweralkylamino or cyano;

R^{111} and R^{112} are independently halogen, cyano, trifluoromethyl, loweralkanoyl, nitro, loweralkyl, loweralkoxy, carboxy, lowercarbalkoxy, trifuloromethoxy, acetamido, loweralkylthio, loweralkylsulfinyl, loweralkylsulfonyl, trichlorovinyl, trifluoromethylthio, trifluoromethylsulfinyl, or trifluoromethylsulfonyl;

R^{109} is amino, mono or diloweralkyl amino, acetamido, acetimido, ureido, formamido, or guanidino; and

R^{110} is carbamoyl, cyano, carbazoyl, amidino or N-hydroxycarbamoyl; wherein the loweralkyl, loweralkyl containing, loweralkoxy and loweralkanoyl groups contain from 1 to 3 carbon atoms.

[0125] Pyrazole derivatives such as those described in U.S. Patent 6,136,831 can serve as a Cox-2 selective inhibitor of the present invention. Such pyrazole derivatives have the formula shown below in formula **XXII**:



XXII

wherein:

R^{114} is hydrogen or halogen;

R^{115} and R^{116} are each independently hydrogen, halogen, lower alkyl, lower alkoxy, hydroxyl or lower alkanoyloxy;

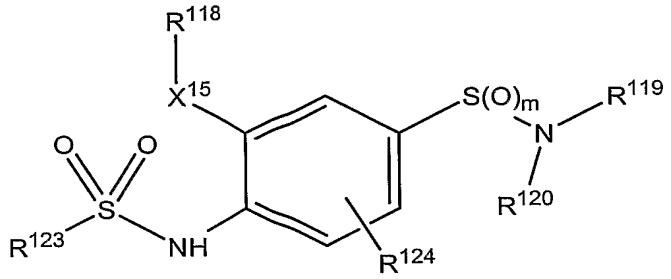
R^{117} is lower haloalkyl or lower alkyl;

X^{14} is sulfur, oxygen or NH; and

Z^6 is lower alkylthio, lower alkylsulfonyl or sulfamoyl;

or a pharmaceutically acceptable salt thereof.

[0126] Materials that can serve as a Cox-2 selective inhibitor of the present invention include substituted derivatives of benzosulphonamides that are described in U.S. Patent 6,297,282. Such benzosulphonamide derivatives have the formula shown below in formula **XXIII**:



XXIII

wherein:

X^{15} denotes oxygen, sulphur or NH;

R^{118} is an optionally unsaturated alkyl or alkyloxyalkyl group, optionally mono- or polysubstituted or mixed substituted by halogen, alkoxy, oxo or cyano, a cycloalkyl, aryl or heteroaryl group optionally mono- or polysubstituted or mixed substituted by halogen, alkyl, CF_3, cyano or alkoxy;

R^{119} and R^{120}, independently from one another, denote hydrogen, an optionally polyfluorised alkyl group, an aralkyl, aryl or heteroaryl group or a group $(CH_2)_n$ –X^{16}; or

R^{119} and R^{120}, together with the N- atom, denote a 3 to 7-membered, saturated, partially or completely unsaturated heterocycle with one or more heteroatoms N, O or S, which can optionally be substituted by oxo, an alkyl, alkylaryl or aryl group, or a group $(CH_2)_n$—X^{16};

X^{16} denotes halogen, NO_2, —OR^{121}, —COR^{121}, —CO_2R^{121}, —OCO_2R^{121}, —CN, —$CONR^{121}OR^{122}$, —$CONR^{121}R^{122}$, —SR^{121}, —$S(O)R^{121}$, —$S(O)_2R^{121}$, —$NR^{121}R^{122}$, —$NHC(O)R^{121}$, —$NHS(O)_2R^{121}$;

n denotes a whole number from 0 to 6;

R^{123} denotes a straight-chained or branched alkyl group with 1-10 C-atoms, a cycloalkyl group, an alkylcarboxyl group, an aryl group, aralkyl group, a heteroaryl or heteroaralkyl group which can optionally be mono- or polysubstituted or mixed substituted by halogen or alkoxy;

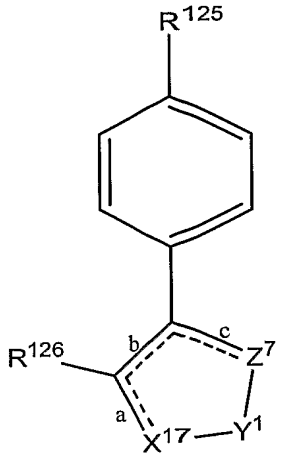
R^{124} denotes halogen, hydroxyl, a straight-chained or branched alkyl, alkoxy, acyloxy or alkyloxycarbonyl group with 1 to 6 carbon atoms, which can optionally be mono- or polysubstituted by halogen, NO_2, —OR^{121}, —COR^{121}, —$CO_2 R^{121}$, —$OCO_2 R^{121}$, —CN, —$CONR^{121} OR^{122}$, —$CONR^{121} R^{122}$, —SR^{121}, —$S(O)R^{121}$, —$S(O)_2 R^{121}$, —$NR^{121} R^{122}$, —$NHC(O)R^{121}$, —$NHS(O)_2 R^{121}$, or a polyfluoroalkyl group;

R^{121} and R^{122}, independently from one another, denote hydrogen, alkyl, aralkyl or aryl; and

m denotes a whole number from 0 to 2;

and the pharmaceutically-acceptable salts thereof.

[0127] Compounds that are useful as Cox-2 selective inhibitors of the present invention include phenyl heterocycles that are described in U.S. Patent Nos. 5,474,995 and 6,239,173. Such phenyl heterocyclic compounds have the formula shown below in formula **XXIV**:



XXIV

or pharmaceutically acceptable salts thereof wherein:

X^{17}—Y^1—Z^7-is selected from the group consisting of

(a) —CH_2 CH_2 CH_2 —,

(b) —$C(O)CH_2$ CH_2 —,

(c) —CH_2 CH_2 C(O)—,

(d) —CR^{129} ($R^{129'}$)—O—C(O)—,

(e) —C(O)—O—CR^{129} ($R^{129'}$)—,

(f) —CH_2 —NR^{127} —CH_2 —,

(g) —CR^{129} ($R^{129'}$)—NR^{127} —C(O)—,

(h) —CR^{128}=$CR^{128'}$ —S—,

(i) —S—CR^{128}=$CR^{128'}$ —,

(j) —S—N=CH—,

(k) —CH=N—S—,

(l) —N=CR^{128} —O—,

(m) —O—CR^{128} =N— ,

(n) —N=CR^{128} —NH—,

(o) —N=CR^{128} —S—, and

(p) —S—CR^{128}=N—,

(q) —C(O)—NR^{127} —CR^{129} ($R^{129'}$)—,

(r) —R^{127} N—CH=CH— provided R^{122} is not —$S(O)_2CH_3$,

(s) —CH=CH—NR^{127} — provided R^{125} is not —$S(O)_2CH_3$;

when side b is a double bond, and sides a and c are single bonds; and

X^{17}—Y^1—Z^7-is selected from the group consisting of

(a) =CH—O—CH=, and

(b) =CH—NR^{127} —CH=,

(c) =N—S—CH=,

(d) =CH—S—N=,

(e) =N—O—CH=,

(f) =CH—O—N=,

(g) =N—S—N=,

(h) =N—O—N=,

when sides a and c are double bonds and side b is a single bond;

R^{125} is selected from the group consisting of

(a) $S(O)_2$ CH_3,

(b) $S(O)_2$ NH_2,

(c) $S(O)_2$ $NHC(O)CF_3$,

(d) $S(O)(NH)CH_3$,

(e) $S(O)(NH)NH_2$,

(f) $S(O)(NH)NHC(O)CF_3$,

(g) $P(O)(CH_3)OH$, and

(h) $P(O)(CH_3)NH_2$;

R^{126} is selected from the group consisting of

(a) C_1 –C_6 alkyl,

(b) C_3, C_4, C_5, C_6, and C_7, cycloalkyl,

(c) mono-, di- or tri-substituted phenyl or naphthyl, wherein the substituent is selected from the group consisting of

(1) hydrogen,

(2) halo,

(3) C_1 –C_6 alkoxy,

(4) C_1 –C_6 alkylthio,

(5) CN,

(6) CF_3,

(7) C_1 –C_6 alkyl,

(8) N_3,

(9) —CO_2 H,

(10) —CO_2 —C_1 –C_4 alkyl,

(11) —$C(R^{129})(R^{130})$—OH,

(12) —$C(R^{129})(R^{130})$—O—C_1 –C_4 alkyl, and

(13) —C_1 –C_6 alkyl-CO_2 —R^{129} ;

(d) mono-, di- or tri-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additionally N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said substituents are selected from the group consisting of

(1) hydrogen,

(2) halo, including fluoro, chloro, bromo and iodo,

(3) C_1 –C_6 alkyl,

(4) C_1 –C_6 alkoxy,

(5) C_1 –C_6 alkylthio,

(6) CN,

(7) CF_3,

(8) N_3,

(9) —$C(R^{129})(R^{130})$—OH, and

(10) —$C(R^{129})(R^{130})$—O—C_1 –C_4 alkyl;

(e) benzoheteroaryl which includes the benzo fused analogs of (d);

R^{127} is selected from the group consisting of

(a) hydrogen,

(b) CF_3,

(c) CN,

(d) C_1 –C_6 alkyl,

(e) hydroxyl C_1 –C_6 alkyl,

(f) —C(O)— C_1 –C_6 alkyl,

(g) optionally substituted:

(1) —C_1 –C_5 alkyl-Q^5,

(2) —C_1 –C_5 alkyl-O—C_1 –C_3 alkyl-Q^5,

(3) —C_1 –C_3 alkyl-S—C_1 –C_3 alkyl-Q^5,

(4) —C_1 –C_5 alkyl-O—Q^5, or

(5) —C_1 –C_5 alkyl-S—Q^5,

wherein the substituent resides on the alkyl and the substituent is C_1 – C_3 alkyl;

(h) –Q^5;

R^{128} and $R^{128'}$ are each independently selected from the group consisting of

(a) hydrogen,

(b) CF_3,

(c) CN,

(d) C_1 –C_6 alkyl,

(e) –Q^5,

(f) —O—Q^5;

(g) —S—Q^5, and

(h) optionally substituted:

(1) —C_1 –C_5 alkyl-Q^5,

(2) —O—C_1 –C_5 alkyl-Q^5,

(3) —S—C_1 –C_5 alkyl-Q^5,

(4) —C_1 –C_3 alkyl-O—C_1 –C_3 alkyl-Q^5,

(5) —C_1 –C_3 alkyl-S—C_1 –C_3 alkyl-Q^5,

(6) —C_1 –C_5 alkyl-O—Q^5,

(7) —C_1 –C_5 alkyl-S—Q^5,

wherein the substituent resides on the alkyl and the substituent is C_1 – C_3 alkyl, and

R^{129}, $R^{129'}$, R^{130}, R^{131} and R^{132} are each independently selected from the group consisting of

(a) hydrogen,

(b) C_1 –C_6 alkyl;

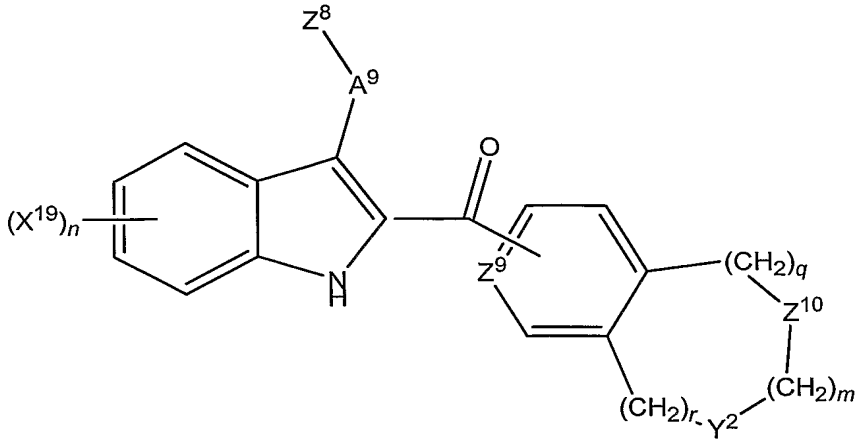
or R^{129} and R^{130} or R^{131} and R^{132} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

Q^5 is CO_2 H, CO_2 —C_1 –C_4 alkyl, tetrazolyl-5-yl, $C(R^{131})(R^{132})(OH)$, or $C(R^{131})(R^{132})$(O—C_1 –C_4 alkyl);

provided that when X—Y—Z is —S—CR^{128}=$CR^{128'}$, then R^{128} and $R^{128'}$ are other than CF_3.

[0128] An exemplary phenyl heterocycle that is disclosed in U.S. Patent No. 6,239,173 is 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(2H)-furanone.

[0129] Bicycliccarbonyl indole compounds such as those described in U.S. Patent No. 6,303,628 are useful as Cox-2 selective inhibitors of the present invention. Such bicycliccarbonyl indole compounds have the formula shown below in formula **XXV**:



XXV

or the pharmaceutically acceptable salts thereof wherein:

A^9 is C_1 –C_6 alkylene or —NR^{133} —;

Z^8 is $C(=L^3)R^{134}$, or SO_2 R^{135} ;

Z^9 is CH or N;

Z^{10} and Y^2 are independently selected from —CH_2 —, O, S and —N—R^{133};

m is 1, 2 or 3;

q and r are independently 0, 1 or 2;

X^{18} is independently selected from halogen, C_1 –C_4 alkyl, halo-substituted C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halo-substituted C_1 –C_4 alkoxy, C_1 –C_4 alkylthio, nitro, amino, mono- or di-(C_1 –C_4 alkyl)amino and cyano;

n is 0, 1, 2, 3 or 4;

L^3 is oxygen or sulfur;

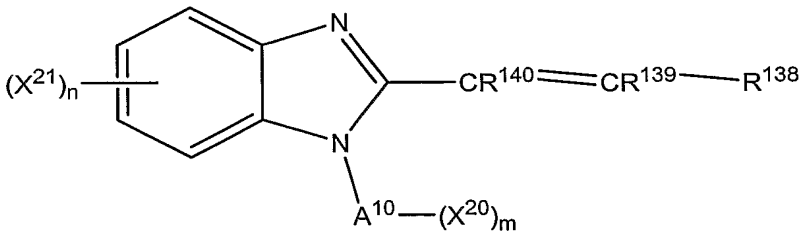
R^{133} is hydrogen or C_1 –C_4 alkyl;

R^{134} is hydroxyl, C_1 –C_6 alkyl, halo-substituted C_1 –C_6 alkyl, C_1 –C_6 alkoxy, halo-substituted C_1 –C_6 alkoxy, C_3 –C_7 cycloalkoxy, C_1 –C_4 alkyl(C_3 –C_7 cycloalkoxy), —NR^{136} R^{137}, C_1 –C_4 alkylphenyl-O— or phenyl-O—, said phenyl being optionally substituted with one to five substituents independently selected from halogen, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy and nitro;

R^{135} is C_1 –C_6 alkyl or halo-substituted C_1 –C_6 alkyl; and

R^{136} and R^{137} are independently selected from hydrogen, C_{1-6} alkyl and halo-substituted C_1 –C_6 alkyl.

[0130] Materials that can serve as a Cox-2 selective inhibitor of the present invention include benzimidazole compounds that are described in U.S. Patent No. 6,310,079. Such benzimidazole compounds have the formula shown below in formula **XXVI**:



XXVI

or a pharmaceutically acceptable salt thereof, wherein:

A^{10} is heteroaryl selected from:

a 5-membered monocyclic aromatic ring having one hetero atom selected from O, S and N and optionally containing one to three N atom(s) in addition to said hetero atom, or

a 6-membered monocyclic aromatic ring having one N atom and optionally containing one to four N atom(s) in addition to said N atom; and said heteroaryl being connected to the nitrogen atom on the benzimidazole through a carbon atom on the heteroaryl ring;

X^{20} is independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 – C_4 alkoxy, halo-substituted C_1 –C_4 alkyl, hydroxyl-substituted C_1 –C_4 alkyl, (C_1 –C_4 alkoxy)C_1 –C_4 alkyl, halo-substituted C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino, N, N-di(C_1 –C_4 alkyl)amino, [N-(C_1 –C_4 alkyl)amino]C_1 – C_4 alkyl, [N, N-di(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, N-(C_1 –C_4 alkanoyl)amonio, N-(C_1 –C_4 alkyl)(C_1 –C_4 alkanoyl)amino, N-[(C_1 —C_4 alkyl)sulfonyl]amino, N-[(halo-substituted C_1 –C_4 alkyl)sulfonyl]amino, C_1 – C_4 alkanoyl, carboxy, (C_1 –C_4 alkoxy)carbonyl, carbamoyl, [N-(C_1 —C_4 alkyl)amino]carbonyl, [N, N-di(C_1 –C_4 alkyl)amino]carbonyl, cyano, nitro, mercapto, (C_1 –C_4 alkyl)thio, (C_1 –C_4 alkyl)sulfinyl, (C_1 –C_4 alkyl)sulfonyl, aminosulfonyl, [N-(C_1 –C_4 alkyl)amino]sulfonyl and [N, N-di(C_1 –C_4 alkyl)amino]sulfonyl;

X^{21} is independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 – C_4 alkoxy, halo-substituted C_1 –C_4 alkyl, hydroxyl-substituted C_1 –C_4 alkyl,

(C_1 –C_4 alkoxy)C_1 –C_4 alkyl, halo-substituted C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino, N, N-di(C_1 –C_4 alkyl)amino, [N-(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, [N, N-di(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, N-(C_1 –C_4 alkanoyl)amino, N-(C_1 –C_4 alkyl)-N-(C_1 –C_4 alkanoyl) amino, N-[(C_1 –C_4 alkyl)sulfonyl]amino, N-[(halo-substituted C_1 –C_4 alkyl)sulfonyl]amino, C_1 –C_4 alkanoyl, carboxy, (C_1 –C_4 alkoxy)hydroxyl, cabamoyl, [N-(C_1 –C_4 alkyl) amino]carbonyl, [N, N-di(C_1 –C_4 alkyl)amino]carbonyl, N-carbomoylamino, cyano, nitro, mercapto, (C_1 –C_4 alkyl)thio, (C_1 –C_4 alkyl)sulfinyl, (C_1 –C_4 alkyl)sulfonyl, aminosulfonyl, [N-(C_1 –C_4 alkyl)amino]sulfonyl and [N, N-di(C_1 –C_4 alkyl)amino]sulfonyl;

R^{138} is selected from hydrogen; straight or branched C_1 –C_4 alkyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, hydroxyl, C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino and N, N-di(C_1 –C_4 alkyl)amino; C_3 –C_8 cycloalkyl optionally substituted with one to three substituent(s) wherein said substituents are indepently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino and N, N-di(C_1 –C_4 alkyl)amino; C_4 –C_8 cycloalkenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino and N, N-di(C_1 –C_4 alkyl)amino; phenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halo-substituted C_1 –C_4 alkyl, hydroxyl-substituted C_1 –C_4 alkyl, (C_1 –C_4 alkoxy)C_1 –C_4 alkyl, halo-substituted C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino, N, N-di(C_1 –C_4 alkyl)amino, [N-(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, [N, N-di(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, N-(C_1 –C_4 alkanoyl)amino, N-[C_1 –C_4 alkyl)(C_1 –C_4 alkanoyl)]amino, N-[(C_1 –C_4 alkyl)sulfony]amino, N-[(halo-substituted C_1 –C_4 alkyl)sulfonyl]amino, C_1 –C_4 alkanoyl, carboxy, (C_1 –C_4 alkoxy)carbonyl, carbomoyl, [N-(C_1 –C_4 alky)amino]carbonyl, [N, N-di(C_1 –C_4 alkyl)amino]carbonyl, cyano, nitro, mercapto, (C_1 –C_4 alkyl)thio, (C_1 –C_4

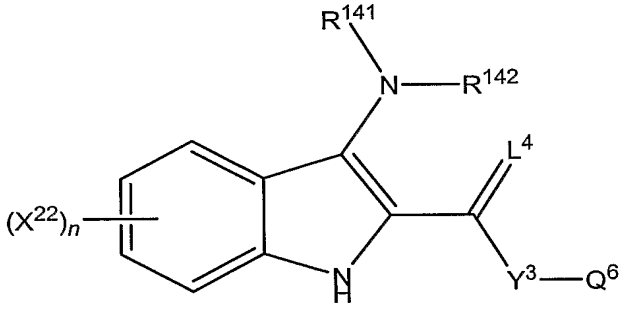
alkyl)sulfinyl, (C_1 –C_4 alkyl)sulfonyl, aminosulfonyl, [N-(C_1 –C_4 alkyl)amino]sulfonyl and [N, N-di(C_1 –C_4 alkyl)amino]sulfonyl; and heteroaryl selected from: a 5-membered monocyclic aromatic ring having one hetero atom selected from O, S and N and optionally containing one to three N atom(s) in addition to said hetero atom; or a 6-membered monocyclic aromatic ring having one N atom and optionally containing one to four N atom(s) in addition to said N atom; and said heteroaryl being optionally substituted with one to three substituent(s) selected from X^{20} ;

R^{139} and R^{140} are independently selected from: hydrogen; halo; C_1 – C_4 alkyl; phenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino and N, N-di(C_1 –C_4 alkyl)amino; or R^{138} and R^{139} can form, together with the carbon atom to which they are attached, a C_3 –C_7 cycloalkyl ring;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1, 2, 3 or 4.

[0131] Compounds that may be employed as a Cox-2 selective inhibitor of the present invention include indole compounds that are described in U.S. Patent No. 6,300,363. Such indole compounds have the formula shown below in formula **XXVII**:



XXVII

and the pharmaceutically acceptable salts thereof, wherein:

L^4 is oxygen or sulfur;

Y^3 is a direct bond or C_1 –C_4 alkylidene;

Q^6 is:

(a) C_1 –C_6 alkyl or halosubstituted C_1 –C_6 alkyl, said alkyl being optionally substituted with up to three substituents independently selected from hydroxyl, C_1 –C_4 alkoxy, amino and mono- or di-(C_1 –C_4 alkyl)amino,

(b) C_3 –C_7 cycloalkyl optionally substituted with up to three substituents independently selected from hydroxyl, C_1 –C_4 alkyl and C_1 –C_4 alkoxy,

(c) phenyl or naphthyl, said phenyl or naphthyl being optionally substituted with up to four substituents independently selected from:

(c-1) halo, C_1 –C_4 alkyl, halosubstituted C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halosubstituted C_1 –C_4 alkoxy, $S(O)_m R^{143}$, $SO_2 NH_2$, $SO_2 N(C_1$ –C_4 alkyl)$_2$, amino, mono- or di-(C_1 –C_4 alkyl)amino, $NHSO_2 R^{143}$, $NHC(O)R^{143}$, CN, $CO_2 H$, CO_2 (C_1 –C_4 alkyl), C_1 –C_4 alkyl-OH, C_1 –C_4 alkyl-OR^{143}, $CONH_2$, $CONH(C_1$ –C_4 alkyl), $CON(C_1$ –C_4 alkyl)$_2$ and —O—Y-phenyl, said phenyl being optionally substituted with one or two substituents independently selected from halo, C_1 –C_4 alkyl, CF_3, hydroxyl, OR^{143}, $S(O)_m R^{143}$, amino, mono- or di-(C_1 –C_4 alkyl)amino and CN;

(d) a monocyclic aromatic group of 5 atoms, said aromatic group having one heteroatom selected from O, S and N and optionally containing up to three N atoms in addition to said heteroatom, and said aromatic group being substituted with up to three substitutents independently selected from:

(d-1) halo, C_1 –C_4 alkyl, halosubstituted C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halosubstituted C_1 –C_4 alkoxy, C_1 –C_4 alkyl-OH, $S(O)_m R^{143}$, $SO_2 NH_2$, $SO_2 N(C_1$ –C_4 alkyl)$_2$, amino, mono- or di-(C_1 –C_4 alkyl)amino, $NHSO_2 R^{143}$, $NHC(O)R^{143}$, CN, $CO_2 H$, CO_2 (C_1 –C_4 alkyl), C_1 –C_4 alkyl-OR^{143}, $CONH_2$, $CONH(C_1$ –C_4 alkyl), $CON(C_1$ –C_4 alkyl)$_2$, phenyl, and mono-, di- or tri-substituted phenyl wherein the substituent is independently selected from halo, CF_3, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, OCF_3, SR^{143}, $SO_2 CH_3$, $SO_2 NH_2$, amino, $C_{1\text{-}4}$ alkylamino and $NHSO_2 R^{143}$;

(e) a monocyclic aromatic group of 6 atoms, said aromatic group having one heteroatom which is N and optionally containing up to three atoms in

addition to said heteroatom, and said aromatic group being substituted with up to three substituents independently selected from the above group (d-1);

R^{141} is hydrogen or C_1 –C_6 alkyl optionally substituted with a substituent selected independently from hydroxyl, OR^{143}, nitro, amino, mono- or di-(C_1 –C_4 alkyl)amino, CO_2H, CO_2 (C_1 –C_4 alkyl), $CONH_2$, $CONH(C_1$ –C_4 alkyl) and $CON(C_1$ –C_4 alkyl)$_2$;

R^{142} is:

(a) hydrogen,

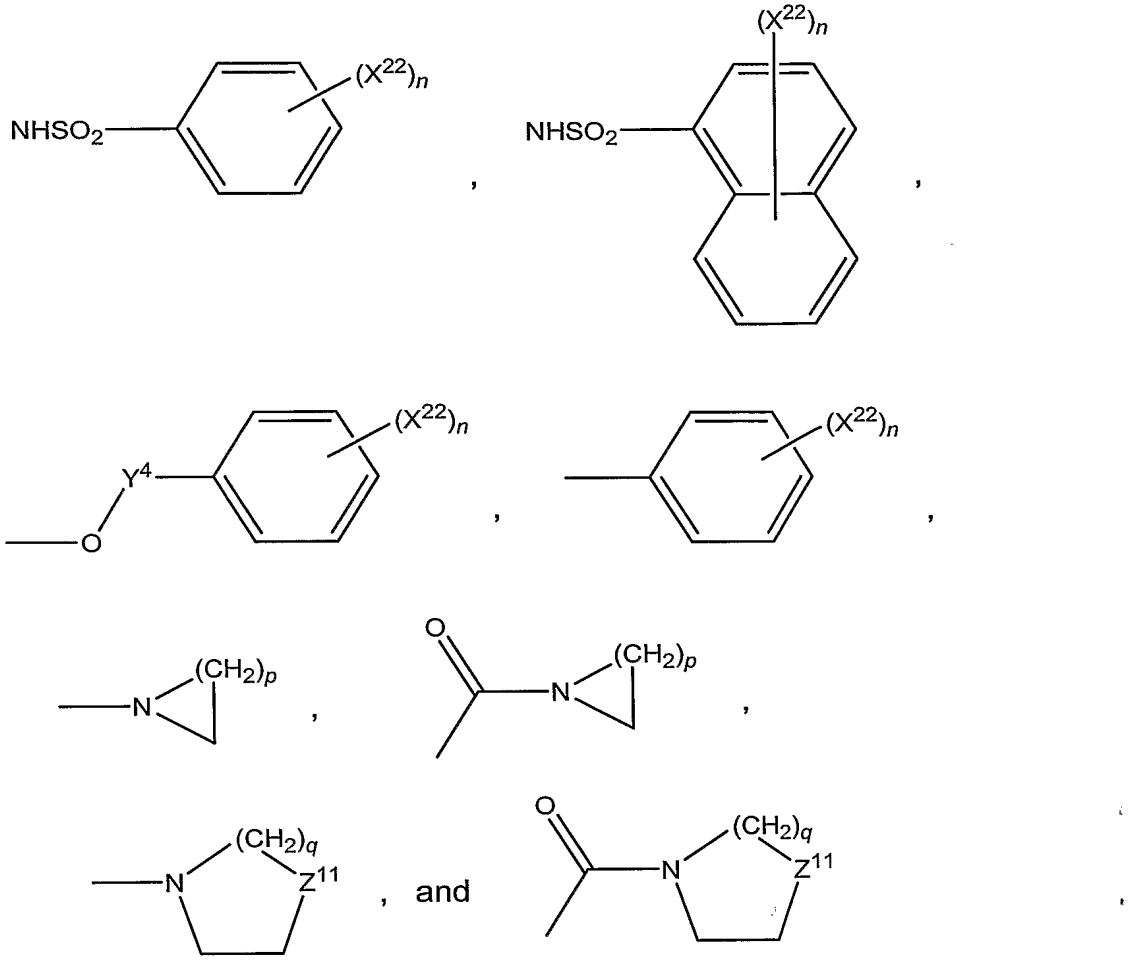
(b) C_1 –C_4 alkyl,

(c) $C(O)R^{145}$,

wherein R^{145} is selected from:

(c-1) C_1 –C_{22} alkyl or C_2 –C_{22} alkenyl, said alkyl or alkenyl being optionally substituted with up to four substituents independently selected from:

(c-1-1) halo, hydroxyl, OR^{143}, $S(O)_m R^{143}$, nitro, amino, mono- or di-(C_1 –C_4 alkyl)amino, $NHSO_2 R^{143}$, CO_2H, CO_2 (C_1 –C_4 alkyl), $CONH_2$, $CONH(C_1$ –C_4 alkyl), $CON(C_1$ –C_4 alkyl)$_2$, $OC(O)R^{143}$, thienyl, naphthyl and groups of the following formulas:



(c-2) C_1 –C_{22} alkyl or C_2 –C_{22} alkenyl, said alkyl or alkenyl being optionally substituted with five to forty-five halogen atoms,

(c-3) –Y^5—C_3 –C_7 cycloalkyl or –Y^5—C_3 –C_7 cycloalkenyl, said cycloalkyl or cycloalkenyl being optionally substituted with up to three substituent independently selected from:

(c-3-1) C_1 –C_4 alkyl, hydroxyl, OR^{143}, $S(O)_m R^{143}$, amino, mono- or di-(C_1 –C_4 alkyl)amino, $CONH_2$, $CONH(C_1$ –C_4 alkyl) and $CON(C_1$ –C_4 alkyl)$_2$,

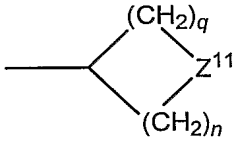
(c-4) phenyl or naphthyl, said phenyl or naphthyl being optionally substituted with up to seven (preferably up to seven) substituents independently selected from:

(c-4-1) halo, C_1 –C_8 alkyl, C_1 –C_4 alkyl-OH, hydroxyl, C_1 –C_8 alkoxy, halosubstituted C_1 –C_8 alkyl, halosubstituted C_1 –C_8 alkoxy, CN, nitro, $S(O)_m R^{143}$, $SO_2 NH_2$, $SO_2 NH(C_1$ –C_4 alkyl), $SO_2 N(C_1$ —C_4 alkyl)$_2$, amino, C_1 –C_4 alkylamino, di-(C_1 –C_4 alkyl)amino, $CONH_2$, $CONH(C_1$ –C_4 alkyl), $CON(C_1$ –C_4 alkyl)$_2$, $OC(O)R^{143}$, and phenyl optionally substituted with up to three substituents independently selected from halo, C_1 –C_4 alkyl, hydroxyl, OCH_3, CF_3, OCF_3, CN, nitro, amino, mono- or di-(C_1 –C_4 alkyl)amino, CO_2 H, CO_2 (C_1 –C_4 alkyl) and $CONH_2$,

(c-5) a monocyclic aromatic group as defined in (d) and (e) above, said aromatic group being optionally substituted with up to three substituents independently selected from:

(c-5-1) halo, C_1 –C_8 alkyl, C_1 –C_4 alkyl-OH, hydroxyl, C_1 –C_8 alkoxy, CF_3, OCF_3, CN, nitro, $S(O)_m R^{143}$, amino, mono- or di-(C_1 –C_4 alkyl)amino, $CONH_2$, $CONH(C_1$ –C_4 alkyl), $CON(C_1$ –C_4 alkyl)$_2$, CO_2 H and CO_2 (C_1 –C_4 alkyl), and —Y-phenyl, said phenyl being optionally substituted with up to three substituents independently selected halogen, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, CF_3, OCF_3, CN, nitro, $S(O)_m R^{143}$, amino, mono- or di-(C_1 –C_4 alkyl)amino, CO_2 H, CO_2 (C_1 –C_4 alkyl), $CONH_2$, $CONH(C_1$ –C_4 alkyl) and $CON(C_1$ –C_4 alkyl)$_2$,

(c-6) a group of the following formula:



X^{22} is halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halosubstituted C_1 –C_4 alkoxy, $S(O)_m R^{143}$, amino, mono- or di-(C_1 –C_4 alkyl)amino, $NHSO_2 R^{143}$, nitro, halosubstitutued C_1 –C_4 alkyl, CN, CO_2 H, CO_2 (C_1 –C_4 alkyl), C_1 –C_4 alkyl-OH, C_1 –C_4 alkylOR^{143}, $CONH_2$, $CONH(C_1$ –C_4 alkyl) or $CON(C_1$ –C_4 alkyl)$_2$;

R^{143} is C_1 –C_4 alkyl or halosubstituted C_1 –C_4 alkyl;

m is 0, 1 or 2; n is 0, 1, 2 or 3; p is 1, 2, 3, 4 or 5; q is 2 or 3;

Z^{11} is oxygen, sulfur or NR^{144} ; and

R^{144} is hydrogen, C_1 –C_6 alkyl, halosubstitutued C_1 –C_4 alkyl or –Y^5-phenyl, said phenyl being optionally substituted with up to two substituents independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, $S(O)_m R^{143}$, amino, mono- or di-(C_1 –C_4 alkyl)amino, CF_3, OCF_3, CN and nitro;

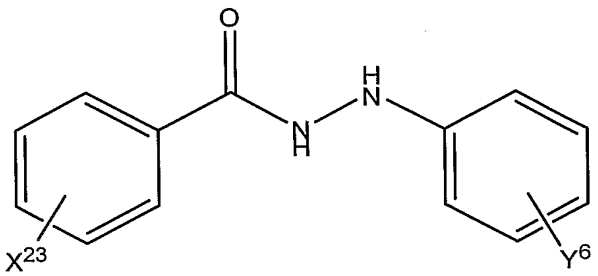
with the proviso that a group of formula –Y^5—Q is not methyl or ethyl when X^{22} is hydrogen;

L^4 is oxygen;

R^{141} is hydrogen; and

R^{142} is acetyl.

[0132] Aryl phenylhydrazides that are described in U.S. Patent No. 6,077,869 can serve as Cox-2 selective inhibitors of the present invention. Such aryl phenylhydrazides have the formula shown below in formula **XXVIII**:



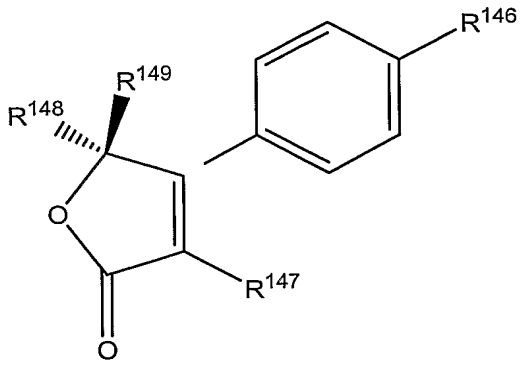
XXVIII

wherein:

X^{23} and Y^6 are selected from hydrogen, halogen, alkyl, nitro, amino, hydroxy, methoxy and methylsulfonyl;

or a pharmaceutically acceptable salt thereof,.

[0133] Materials that can serve as a Cox-2 selective inhibitor of the present invention include 2-aryloxy, 4-aryl furan-2-ones that are described in U.S. Patent No. 6,140,515. Such 2-aryloxy, 4-aryl furan-2-ones have the formula shown below in formula **XXIX**:



XXIX

or a pharmaceutical salt thereof, wherein:

R^{146} is selected from the group consisting of SCH_3, —$S(O)_2$ CH_3 and —$S(O)_2$ NH_2 ;

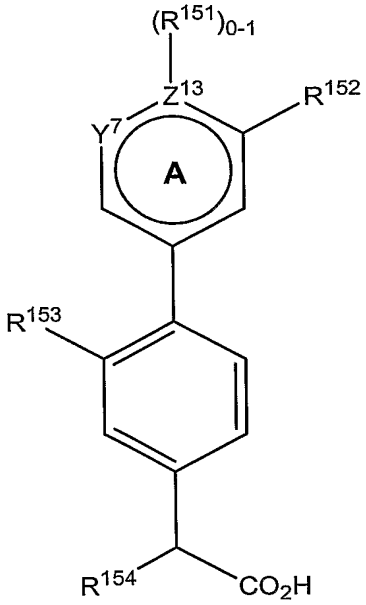
R^{147} is selected from the group consisting of OR^{150}, mono or di-substituted phenyl or pyridyl wherein the substituents are selected from the group consisting of methyl, chloro and F;

R^{150} is unsubstituted or mono or di-substituted phenyl or pyridyl wherein the substituents are selected from the group consisting of methyl, chloro and F;

R^{148} is H, C_1 –C_4 alkyl optionally substituted with 1 to 3 groups of F, Cl or Br; and

R^{149} is H, C_1 –C_4 alkyl optionally substituted with 1 to 3 groups of F, Cl or Br, with the proviso that R^{148} and R^{149} are not the same.

[0134] Materials that can serve as a Cox-2 selective inhibitor of the present invention include bisaryl compounds that are described in U.S. Patent No. 5,994,379. Such bisaryl compounds have the formula shown below in formula **XXX**:



XXX

or a pharmaceutically acceptable salt, ester or tautomer thereof, wherein:

Z^{13} is C or N;

when Z^{13} is N, R^{151} represents H or is absent, or is taken in conjunction with R^{152} as described below:

when Z^{13} is C, R^{151} represents H and R^{152} is a moiety which has the following characteristics:

(a) it is a linear chain of 3-4 atoms containing 0-2 double bonds, which can adopt an energetically stable transoid configuration and if a double bond is present, the bond is in the trans configuration,

(b) it is lipophilic except for the atom bonded directly to ring A, which is either lipophilic or non-lipophilic, and

(c) there exists an energetically stable configuration planar with ring A to within about 15 degrees;

or R^{151} and R^{152} are taken in combination and represent a 5- or 6-membered aromatic or non-aromatic ring D fused to ring A, said ring D containing 0-3 heteroatoms selected from O, S and N;

said ring D being lipophilic except for the atoms attached directly to ring A, which are lipophilic or non-lipophilic, and said ring D having available an

energetically stable configuration planar with ring A to within about 15 degrees;

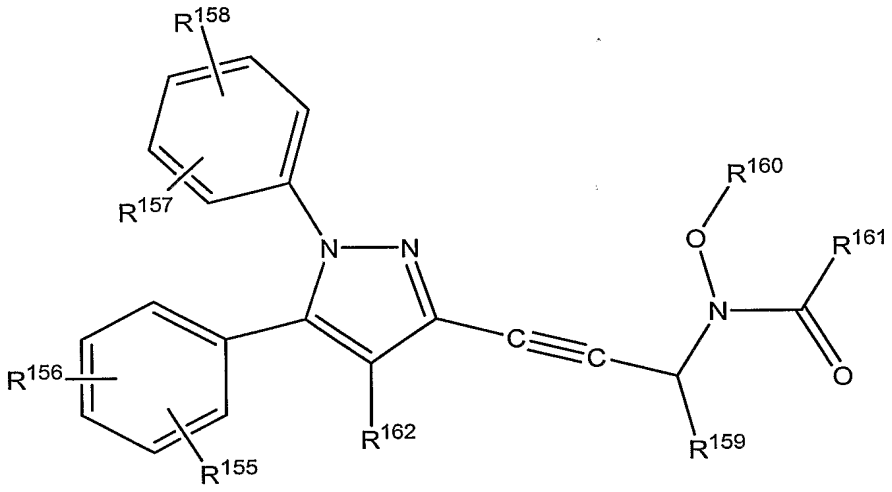
said ring D further being substituted with 1 R^a group selected from the group consisting of C_1 –C_2 alkyl, —OC_1 –C_2 alkyl, —NHC_1 –C_2 alkyl, —$N(C_1$ –C_2 alkyl$)_2$, —C(O) C_1 –C_2 alkyl, —S—C_1 –C_2 alkyl and —C(S) C_1 –C_2 alkyl;

Y^7 represents N, CH or C—OC_1 –C_3 alkyl, and when Z^{13} is N, Y^7 can also represent a carbonyl group;

R^{153} represents H, Br, Cl or F; and

R^{154} represents H or CH_3.

[0135] Compounds useful as Cox-2 selective inhibitors of the present invention include 1,5-diarylpyrazoles that are described in U.S. Patent No. 6,028,202. Such 1,5-diarylpyrazoles have the formula shown below in formula **XXXI**:



XXXI

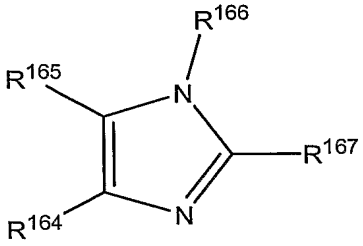
wherein:

R^{155}, R^{156}, R^{157}, and R^{158} are independently selected from the groups consisting of hydrogen, C_1 –C_5 alkyl, C_1 –C_5 alkoxy, phenyl, halo, hydroxyl, C_1 –C_5 alkylsulfonyl, C_1 –C_5 alkylthio, trihaloC_1 –C_5 alkyl, amino, nitro and 2-quinolinylmethoxy;

R^{159} is hydrogen, C_1 –C_5 alkyl, trihaloC_1 –C_5 alkyl, phenyl, substituted phenyl where the phenyl substitutents are halogen, C_1 –C_5 alkoxy,

trihaloC_1 –C_5 alkyl or nitro or R^{159} is heteroaryl of 5-7 ring members where at least one of the ring members is nitrogen, sulfur or oxygen;
R^{160} is hydrogen, C_1 –C_5 alkyl, phenyl C_1 –C_5 alkyl, substituted phenyl C_1 – C_5 alkyl where the phenyl substitutents are halogen, C_1 –C_5 alkoxy, trihaloC_1 –C_5 alkyl or nitro, or R^{160} is C_1 –C_5 alkoxycarbonyl, phenoxycarbonyl, substituted phenoxycarbonyl where the phenyl substitutents are halogen, C_1 –C_5 alkoxy, trihaloC_1 –C_5 alkyl or nitro;
R^{161} is C_1 –C_{10} alkyl, substituted C_1 –C_{10} alkyl where the substituents are halogen, trihaloC_1 –C_5 alkyl, C_1 –C_5 alkoxy, carboxy, C_1 –C_5 alkoxycarbonyl, amino, C_1 –C_5 alkylamino, diC_1 –C_5 alkylamino, diC_1 –C_5 alkylaminoC_1 –C_5 alkylamino, C_1 –C_5 alkylaminoC_1 –C_5 alkylamino or a heterocycle containing 4-8 ring atoms where one more of the ring atoms is nitrogen, oxygen or sulfur, where said heterocycle may be optionally substituted with C_1 –C_5 alkyl; or R^{161} is phenyl, substituted phenyl (where the phenyl substitutents are one or more of C_1 –C_5 alkyl, halogen, C_1 –C_5 alkoxy, trihaloC_1 –C_5 alkyl or nitro), or R^{161} is heteroaryl having 5-7 ring atoms where one or more atoms are nitrogen, oxygen or sulfur, fused heteroaryl where one or more 5-7 membered aromatic rings are fused to the heteroaryl; or
R^{161} is NR^{163} R^{164} where R^{163} and R^{164} are independently selected from hydrogen and $C_{1\text{-}5}$ alkyl or R^{163} and R^{164} may be taken together with the depicted nitrogen to form a heteroaryl ring of 5-7 ring members where one or more of the ring members is nitrogen, sulfur or oxygen where said heteroaryl ring may be optionally substituted with C_1 –C_5 alkyl; R^{162} is hydrogen, C_1 –C_5 alkyl, nitro, amino, and halogen;
and pharmaceutically acceptable salts thereof.

[0136] Materials that can serve as a Cox-2 selective inhibitor of the present invention include 2-substituted imidazoles that are described in U.S. Patent No. 6,040,320. Such 2-substituted imidazoles have the formula shown below in formula **XXXII**:



XXXII

wherein:

R^{164} is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms, or

substituted phenyl;

wherein the substituents are independently selected from one or members of the group consisting of C_{1-5} alkyl, halogen, nitro, trifluoromethyl and nitrile;

R^{165} is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms,

substituted heteroaryl;

wherein the substituents are independently selected from one or more members of the group consisting of C_1 –C_5 alkyl and halogen, or

substituted phenyl,

wherein the substituents are independently selected from one or members of the group consisting of C_1 –C_5 alkyl, halogen, nitro, trifluoromethyl and nitrile;

R^{166} is hydrogen, 2-(trimethylsilyl)ethoxymethyl), C_1 –C_5 alkoxycarbonyl, aryloxycarbonyl, arylC_1 –C_5 alkyloxycarbonyl, arylC_1 –C_5 alkyl, phthalimidoC_1 –C_5 alkyl, aminoC_1 –C_5 alkyl, diaminoC_1 –C_5 alkyl, succinimidoC_1 –C_5 alkyl, C_1 –C_5 alkylcarbonyl, arylcarbonyl, C_1 –C_5 alkylcarbonylC_1 –C_5 alkyl, aryloxycarbonylC_1 –C_5 alkyl, heteroarylC_1 –C_5 alkyl where the heteroaryl contains 5 to 6 ring atoms, or

substituted arylC_1 –C_5 alkyl,

wherein the aryl substituents are independently selected from one or more members of the group consisting of C_1 –C_5 alkyl, C_1 –C_5 alkoxy, halogen, amino, C_1 –C_5 alkylamino, and diC_1 –C_5 alkylamino;

R^{167} is $(A^{11})_n$ –$(CH^{165})_q$ –X^{24} wherein:

A^{11} is sulfur or carbonyl;

n is 0 or 1;

q is 0-9;

X^{24} is selected from the group consisting of hydrogen, hydroxyl, halogen, vinyl, ethynyl, C_1 –C_5 alkyl, C_3 –C_7 cycloalkyl, C_1 –C_5 alkoxy, phenoxy, phenyl, arylC_1 –C_5 alkyl, amino, C_1 –C_5 alkylamino, nitrile, phthalimido, amido, phenylcarbonyl, C_1 –C_5 alkylaminocarbonyl, phenylaminocarbonyl, arylC_1 –C_5 alkylaminocarbonyl, C_1 –C_5 alkylthio, C_1 –C_5 alkylsulfonyl, phenylsulfonyl,

substituted sulfonamido,

wherein the sulfonyl substituent is selected from the group consisting of C_1 –C_5 alkyl, phenyl, araC_1 –C_5 alkyl, thienyl, furanyl, and naphthyl;

substituted vinyl,

wherein the substituents are independently selected from one or members of the group consisting of fluorine, bromine, chlorine and iodine,

substituted ethynyl,

wherein the substituents are independently selected from one or more members of the group consisting of fluorine, bromine chlorine and iodine,

substituted C_1 –C_5 alkyl,

wherein the substituents are selected from the group consisting of one or more C_1 –C_5 alkoxy, trihaloalkyl, phthalimido and amino,

substituted phenyl,

wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_1 –C_5 alkyl, halogen and C_1 –C_5 alkoxy,

substituted phenoxy,

wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_1 –C_5 alkyl, halogen and C_1 –C_5 alkoxy,

substituted C_1 –C_5 alkoxy,

wherein the alkyl substituent is selected from the group consisting of phthalimido and amino,

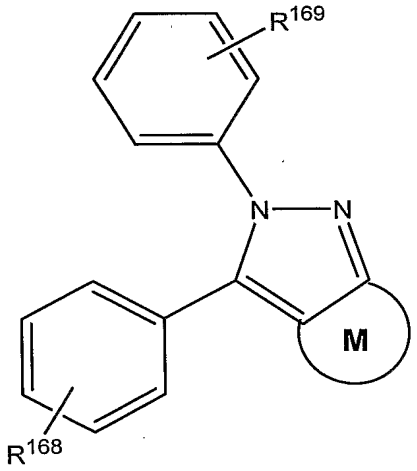
substituted arylC_1 –C_5 alkyl,
wherein the alkyl substituent is hydroxyl,
substituted arylC_1 –C_5 alkyl,
wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_1 –C_5 alkyl, halogen and C_1 –C_5 alkoxy,
substituted amido,
wherein the carbonyl substituent is selected from the group consisting of C_1 –C_5 alkyl, phenyl, arylC_1 –C_5 alkyl, thienyl, furanyl, and naphthyl,
substituted phenylcarbonyl,
wherein the phenyl substituents are independently selected from one or members of the group consisting of C_1 –C_5 alkyl, halogen and C_1 –C_5 alkoxy,
substituted C_1 –C_5 alkylthio,
wherein the alkyl substituent is selected from the group consisting of hydroxyl and phthalimido,
substituted C_1 –C_5 alkylsulfonyl,
wherein the alkyl substituent is selected from the group consisting of hydroxyl and phthalimido,
substituted phenylsulfonyl,
wherein the phenyl substituents are independently selected from one or members of the group consisting of bromine, fluorine, chlorine, C_1 –C_5 alkoxy and trifluoromethyl,
with the proviso:
if A^{11} is sulfur and X^{24} is other than hydrogen, C_1 –C_5 alkylaminocarbonyl, phenylaminocarbonyl, arylC_1 –C_5 alkylaminocarbonyl, C_1 –C_5 alkylsulfonyl or phenylsulfonyl, then q must be equal to or greater than 1;
if A^{11} is sulfur and q is 1, then X^{24} cannot be C_1 –C_2 alkyl;
if A^{11} is carbonyl and q is 0, then X^{24} cannot be vinyl, ethynyl, C_1 –C_5 alkylaminocarbonyl, phenylaminocarbonyl, arylC_1 –C_5 alkylaminocarbonyl, C_1 –C_5 alkylsulfonyl or phenylsulfonyl;

if A^{11} is carbonyl, q is 0 and X^{24} is H, then R^{166} is not 2-(trimethylsilyl)ethoxymethyl;

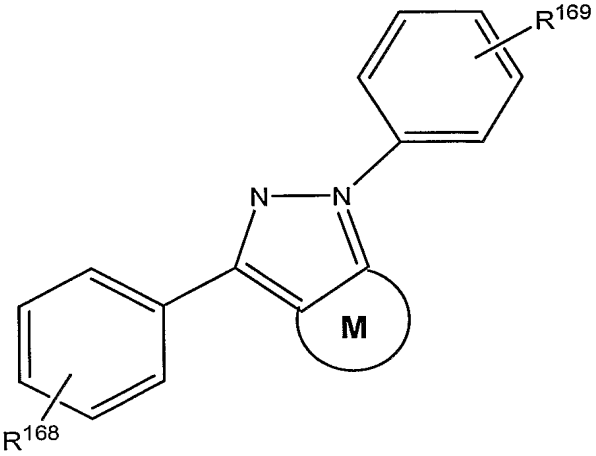
if n is 0 and q is 0, then X^{24} cannot be hydrogen;

and pharmaceutically acceptable salts thereof.

[0137] Materials that can serve as a Cox-2 selective inhibitor of the present invention include 1,3- and 2,3-diarylcycloalkano and cycloalkeno pyrazoles that are described in U.S. Patent No. 6,083,969. Such 1,3- and 2,3-diarylpyrazole compounds have the general formulas shown below in formulas **XXXIII** and **XXXIV**:



XXXIII



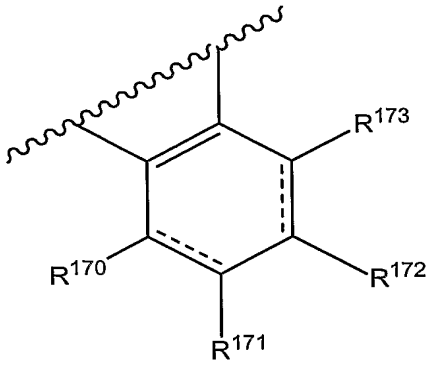
XXXIV

wherein:

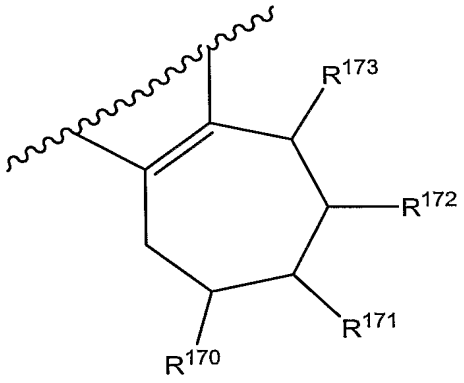
R^{168} and R^{169} are independently selected from the group consisting of hydrogen, halogen, $(C_1 - C_6)$alkyl, $(C_1 - C_6)$alkoxy, nitro, amino, □ydroxyl,

trifluoro, —S(C_1 –C_6)alkyl, —SO(C_1 –C_6)alkyl and —SO_2 (C_1 –C_6)alkyl; and

the fused moiety M is a group selected from the group consisting of an optionally substituted cyclohexyl and cycloheptyl group having the formulae:



,or



wherein:

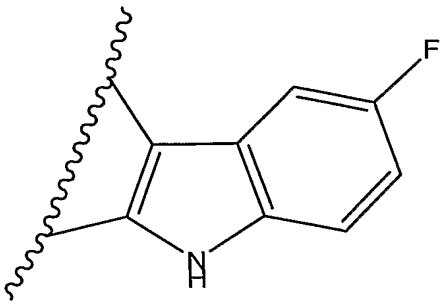
R^{170} is selected from the group consisting of hydrogen, halogen, hydroxyl and carbonyl;

or R^{170} and R^{171} taken together form a moiety selected from the group consisting of —$OCOCH_2$ —, —$ONH(CH_3)COCH_2$ —, —OCOCH= and —O—;

R^{171} and R^{172} are independently selected from the group consisting of hydrogen, halogen, hydroxyl, carbonyl, amino, (C_1 –C_6)alkyl, (C_1 –C_6)alkoxy, =NOH, —NR^{174} R^{175}, —OCH_3, —OCH_2 CH_3, —OSO_2 $NHCO_2$ CH_3, =$CHCO_2$ CH_2 CH_3, —CH_2 CO_2 H, —CH_2 CO_2 CH_3, —CH_2 CO_2 CH_2 CH_3, —CH_2 $CON(CH_3)_2$, —CH_2 CO_2 $NHCH_3$, —$CHCHCO_2$ CH_2 CH_3, —$OCON(CH_3)OH$, —$C(COCH_3)_2$, di(C_1 –C_6)alkyl and di(C_1 –C_6)alkoxy;

R^{173} is selected from the group consisting of hydrogen, halogen, hydroxyl, carbonyl, amino, (C_1 –C_6)alkyl, (C_1 –C_6)alkoxy and optionally substituted carboxyphenyl, wherein substituents on the carboxyphenyl group are selected from the group consisting of halogen, hydroxyl, amino, (C_1 –C_6)alkyl and (C_1 –C_6)alkoxy;

or R^{172} and R^{173} taken together form a moiety selected from the group consisting of —O—and



R^{174} is selected from the group consisting of hydrogen, OH, —$OCOCH_3$, —$COCH_3$ and (C_1 –C_6)alkyl; and

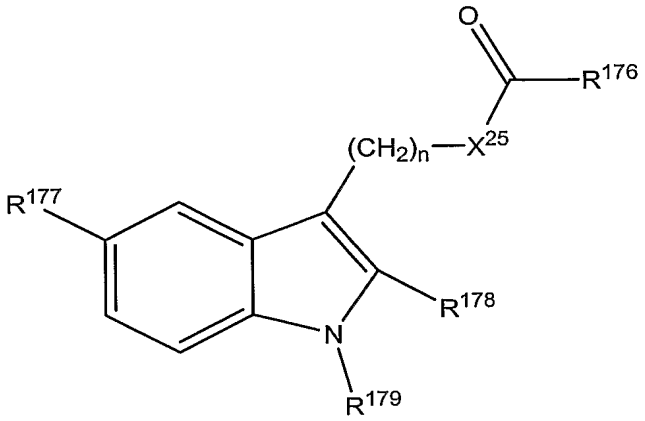
R^{175} is selected from the group consisting of hydrogen, OH, —$OCOCH_3$, —$COCH_3$, (C_1 –C_6)alkyl, —$CONH_2$ and —SO_2 CH_3 ;

with the proviso that

if M is a cyclohexyl group, then R^{170} through R^{173} may not all be hydrogen; and

pharmaceutically acceptable salts, esters and pro-drug forms thereof.

[0138] Esters derived from indolealkanols and novel amides derived from indolealkylamides that are described in U.S. Patent No. 6,306,890 can serve as Cox-2 selective inhibitors of the present invention. Such compounds have the general formula shown below in formula **XXXV**:



XXXV

wherein:

R^{176} is C_1 –C_6 alkyl, C_1 –C_6 branched alkyl, C_4 –C_8 cycloalkyl, C_1 –C_6 hydroxyalkyl, branched C_1 –C_6 hydroxyalkyl, hydroxyl substituted C_4 –C_8

aryl, primary, secondary or tertiary C_1 –C_6 alkylamino, primary, secondary or tertiary branched C_1 –C_6 alkylamino, primary, secondary or tertiary C_4 –C_8 arylamino, C_1 –C_6 alkylcarboxylic acid, branched C_1 –C_6 alkylcarboxylic acid, C_1 –C_6 alkylester, branched C_1 –C_6 alkylester, C_4 –C_8 aryl, C_4 –C_8 arylcarboxylic acid, C_4 –C_8 arylester, C_4 –C_8 aryl substituted C_1 –C_6 alkyl, C_4 –C_8 heterocyclic alkyl or aryl with O, N or S in the ring, alkyl-substituted or aryl-substituted C_4 –C_8 heterocyclic alkyl or aryl with O, N or S in the ring, or halo-substituted versions thereof, where halo is chloro, bromo, fluoro or iodo;

R^{177} is C_1 –C_6 alkyl, C_1 –C_6 branched alkyl, C_4 –C_8 cycloalkyl, C_4 –C_8 aryl, C_4 –C_8 aryl-substituted C_1 –C_6 alkyl, C_1 –C_6 alkoxy, C_1 –C_6 branched alkoxy, C_4 –C_8 aryloxy, or halo-substituted versions thereof or R^{177} is halo where halo is chloro, fluoro, bromo, or iodo;

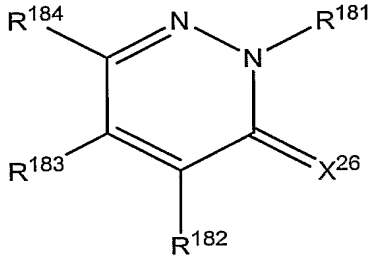
R^{178} is hydrogen, C_1 –C_6 alkyl or C_1 –C_6 branched alkyl;

R^{179} is C_1 –C_6 alkyl, C_4 –C_8 aroyl, C_4 –C_8 aryl, C_4 –C_8 heterocyclic alkyl or aryl with O, N or S in the ring, C_4 –C_8 aryl-substituted C_1 –C_6 alkyl, alkyl-substituted or aryl-substituted C_4 –C_8 heterocyclic alkyl or aryl with O, N or S in the ring, alkyl-substituted C_4 –C_8 aroyl, or alkyl-substituted C_4 –C_8 aryl, or halo-substituted versions thereof where halo is chloro, bromo, or iodo;

n is 1, 2, 3, or 4; and

X^{25} is O, NH, or N—R^{180}, where R^{180} is C_1 –C_6 or C_1 –C_6 branched alkyl.

[0139] Materials that can serve as a Cox-2 selective inhibitor of the present invention include pyridazinone compounds that are described in U.S. Patent No. 6,307,047. Such pyridazinone compounds have the formula shown below in formula **XXXVI**:



XXXVI

or a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein:

X^{26} is selected from the group consisting of O, S, —NR^{185}, —NOR^{a}, and –NNR^{b} R^{c} ;

R^{185} is selected from the group consisting of alkenyl, alkyl, aryl, arylalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclic, and heterocyclic alkyl;

R^{a}, R^{b}, and R^{c} are independently selected from the group consisting of alkyl, aryl, arylalkyl, cycloalkyl, and cycloalkylalkyl;

R^{181} is selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxyiminoalkoxy, alkyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkynyl, arylhaloalkyl, arylhydroxyalkyl, aryloxy, aryloxyhaloalkyl, aryloxyhydroxyalkyl, arylcarbonylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylidenealkyl, haloalkenyl, haloalkoxyhydroxyalkyl, haloalkyl, haloalkynyl, heterocyclic, heterocyclic alkoxy, heterocyclic alkyl, heterocyclic oxy, hydroxyalkyl, hydroxyiminoalkoxy, —$(CH_2)_n$ $C(O)R^{186}$, —$(CH_2)_n$ $CH(OH)R^{186}$, —$(CH_2)_n$ $C(NOR^{d})R^{186}$, —$(CH_2)_n$ $CH(NOR^{d})R^{186}$, —$(CH_2)_n$ $CH(NR^{d}\ R^{e})R^{186}$, —R^{187} R^{188}, —$(CH_2)_n$ $C{\equiv}CR^{188}$, —$(CH_2)_n$ $[CH(CX^{26'}{}_3)]_m$ $(CH_2)_p$ R^{188}, —$(CH_2)_n$ $(CX^{26'}{}_2)_m$ $(CH_2)_p$ R^{188}, and —$(CH_2)_n$ $(CHX^{26'})_m$ $(CH_2)_m$ R^{188} ;

R^{186} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkenyl, cycloalkyl, haloalkenyl, haloalkyl, haloalkynyl, heterocyclic, and heterocyclic alkyl;

R^{187} is selected from the group consisting of alkenylene, alkylene, halo-substituted alkenylene, and halo-substituted alkylene;

R^{188} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkenyl, haloalkyl, heterocyclic, and heterocyclic alkyl;

R^{d} and R^{e} are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkenyl, cycloalkyl, haloalkyl, heterocyclic, and heterocyclic alkyl;

$X^{26'}$ is halogen;

m is an integer from 0-5;

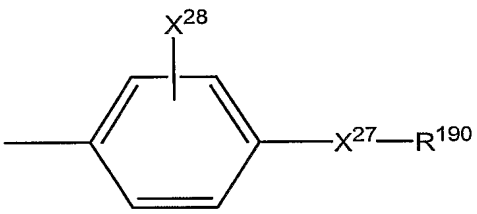
n is an integer from 0-10;

p is an integer from 0-10;

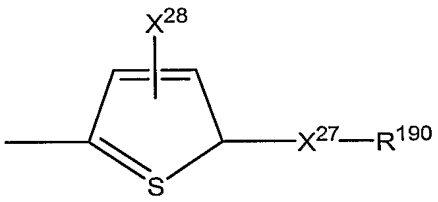
R^{182}, R^{183}, and R^{184} are independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyiminoalkoxy, alkoxyiminoalkyl, alkyl, alkynyl, alkylcarbonylalkoxy, alkylcarbonylamino, alkylcarbonylaminoalkyl, aminoalkoxy, aminoalkylcarbonyloxyalkoxy aminocarbonylalkyl, aryl, arylalkenyl, arylalkyl, arylalkynyl, carboxyalkylcarbonyloxyalkoxy, cyano, cycloalkenyl, cycloalkyl, cycloalkylidenealkyl, haloalkenyloxy, haloalkoxy, haloalkyl, halogen, heterocyclic, hydroxyalkoxy, hydroxyiminoalkoxy, hydroxyiminoalkyl, mercaptoalkoxy, nitro, phosphonatoalkoxy, Y^8, and Z^{14};

provided that one of R^{182}, R^{183}, or R^{184} must be Z^{14}, and further provided that only one of R^{182}, R^{183}, or R^{184} is Z^{14};

Z^{14} is selected from the group consisting of



and



X^{27} is selected from the group consisting of $S(O)_2$, $S(O)(NR^{191})$, $S(O)$, $Se(O)_2$, $P(O)(OR^{192})$, and $P(O)(NR^{193}\ R^{194})$;

X^{28} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl and halogen;

R^{190} is selected from the group consisting of alkenyl, alkoxy, alkyl, alkylamino, alkylcarbonylamino, alkynyl, amino, cycloalkenyl, cycloalkyl, dialkylamino, —$NHNH_2$, and —$NCHN(R^{191})R^{192}$;

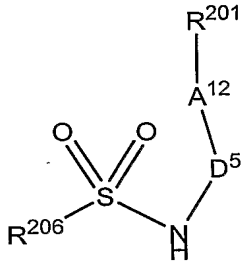
R^{191}, R^{192}, R^{193}, and R^{194} are independently selected from the group consisting of hydrogen, alkyl, and cycloalkyl, or R^{193} and R^{194} can be taken together, with the nitrogen to which they are attached, to form a 3-6 membered ring containing 1 or 2 heteroatoms selected from the group consisting of O, S, and NR^{188} ;

Y^8 is selected from the group consisting of $-OR^{195}$, $—SR^{195}$, $—C(R^{197})(R^{198})R^{195}$, $—C(O)R^{195}$, $—C(O)OR^{195}$, $—N(R^{197})C(O)R^{195}$, $—NC(R^{197})R^{195}$, and $—N(R^{197})R^{195}$;

R^{195} is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkyl, alkylthioalkyl, alkynyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, hydroxyalkyl, and NR^{199} R^{200} ; and

R^{197}, R^{198}, R^{199}, and R^{200} are independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkyl, cycloalkenyl, cycloalkyl, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl.

[0140] Benzosulphonamide derivatives that are described in U.S. Patent No. 6,004,948 are useful as Cox-2 selective inhibitors of the present invention. Such benzosulphonamide derivatives have the formula shown below in formula **XXXVII**:



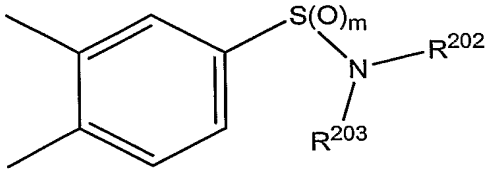
XXXVII

wherein:

A^{12} denotes oxygen, sulphur or NH;

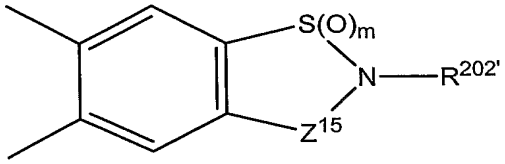
R^{201} denotes a cycloalkyl, aryl or heteroaryl group optionally mono- or polysubstituted by halogen, alkyl, CF_3 or alkoxy;

D^5 denotes a group of formula **XXXVIII** or **XXXIX**:



XXXVIII

or



XXXIX

R^{202} and R^{203} independently of each other denote hydrogen, an optionally polyfluorinated alkyl radical, an aralkyl, aryl or heteroaryl radical or a radical $(CH_2)_n -X^{29}$; or

R^{202} and R^{203} together with the N-atom denote a three- to seven-membered, saturated, partially or totally unsaturated heterocycle with one or more heteroatoms N, O, or S, which may optionally be substituted by oxo, an alkyl, alkylaryl or aryl group or a group $(CH_2)_n -X^{29}$, $R^{202'}$ denotes hydrogen, an optionally polyfluorinated alkyl group, an aralkyl, aryl or heteroaryl group or a group $(CH_2)_n -X^{29}$,

wherein:

X^{29} denotes halogen, NO_2, —OR^{204}, —COR^{204}, —$CO_2 R^{204}$, —$OCO_2 R^{204}$, —CN, —$CONR^{204} OR^{205}$, —$CONR^{204} R^{205}$, —SR^{204}, —$S(O)R^{204}$, —$S(O)_2 R^{204}$, —$NR^{204} R^{205}$, —$NHC(O)R^{204}$, —$NHS(O)_2 R^{204}$;

Z^{15} denotes $-CH_2$ —, —$CH_2 -CH_2$ —, —$CH_2 -CH_2 -CH_2$ —, —CH_2 —CH=CH—, —CH=CH—CH_2 —, —CH_2 —CO—, —CO—CH_2 —, —NHCO—, —CONH—, —$NHCH_2$ —, —CH_2 NH—, —N=CH—, —NHCH—, —CH_2—CH_2—NH—, —CH=CH—, >N—R^{203}, >C=O, >$S(O)_m$;

R^{204} and R^{205} independently of each other denote hydrogen, alkyl, aralkyl or aryl;

n is an integer from 0 to 6;

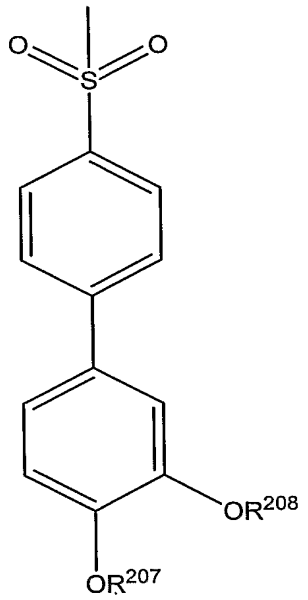
R^{206} is a straight-chained or branched $C_1 -C_4$ alkyl group which may optionally be mono- or polysubstituted by halogen or alkoxy, or R^{206} denotes CF_3; and

m denotes an integer from 0 to 2;

with the proviso that A^{12} does not represent O if R^{206} denotes CF_3;

and the pharmaceutically acceptable salts thereof.

[0141] Materials that can serve as Cox-2 selective inhibitors of the present invention include methanesulfonyl-biphenyl derivatives that are described in U.S. Patent No. 6,583,321. Such methanesulfonyl-biphenyl derivatives have the formula shown below in formula **XXXX**:



XXXX

wherein:

R^{207} and R^{208} are respectively a hydrogen;

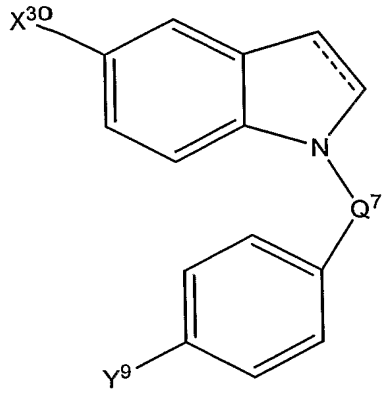
C_1 –C_4-alkyl substituted or not substituted by halogens;

C_3 –C_7-cycloalkyl;

C_1 –C_5-alkyl containing 1-3 ether bonds and/or an aryl substitute; substituted or not substituted phenyl;

or substituted or not substituted five or six ring-cycled heteroaryl containing more than one hetero atoms selected from a group consisting of nitrogen, sulfur, and oxygen (wherein phenyl or heteroaryl can be one- or multi-substituted by a substituent selected from a group consisting of hydrogen, methyl, ethyl, and isopropyl).

[0142] Cox-2 selective inhibitors such as 1H-indole derivatives described in U.S. Patent No. 6,599,929 are useful in the present invention. Such 1H-indole derivatives have the formula shown below in formula **XXXXI**:



XXXXI

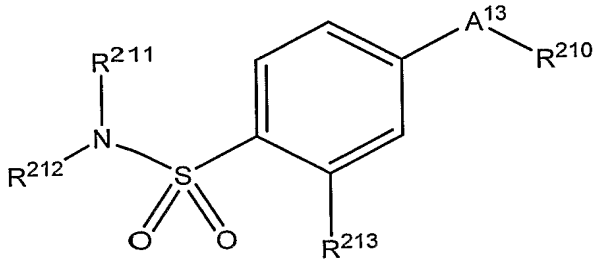
wherein:

X^{30} is $-NHSO_2R^{209}$ wherein R^{209} represents hydrogen or C_1 $-C_3-$ alkyl;

Y^9 is hydrogen, halogen, C_1 $-C_3-$alkyl substituted or not substituted by halogen, NO_2, NH_2, OH, OMe, CO_2H, or CN; and

Q^7 is C=O, C=S, or CH_2.

[0143] Compounds that are useful as Cox-2 selective inhibitors of the present invention include prodrugs of Cox-2 inhibitors that are described in U.S. Patent Nos. 6,436,967 and 6,613,790. Such prodrugs of Cox-2 inhibitors have the formula shown below in formula **XXXXII**:



XXXXII

wherein:

A^{13} is a ring substituent selected from partially unsaturated heterocyclic, heteroaryl, cycloalkenyl and aryl, wherein A^{13} is unsubstituted or substituted with one or more radicals selected from alkylcarbonyl,

formyl, halo, alkyl, haloalkyl, oxo, cyano, nitro, carboxyl, alkoxy, aminocarbonyl, alkoxycarbonyl, carboxyalkyl, cyanoalkyl, hydroxyalkyl, haloalkylsulfonyloxy, alkoxyalkyloxyalkyl, carboxyalkoxyalkyl, cycloalkylalkyl, alkenyl, alkynyl, heterocycloxy, alkylthio, cycloalkyl, aryl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, alkylthioalkyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, araalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, alkylamino, -arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, and N-alkyl-N-arylaminosulfonyl;

R^{210} is selected from heterocyclyl, cycloalkyl, cycloalkenyl, and aryl, wherein R^{210} is unsubstituted or substituted with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy, and alkylthio;

R^{211} is selected from hydrido and alkoxycarbonylalkyl;

R^{212} is selected from alkyl, carboxyalkyl, acyl, alkoxycarbonyl, heteroarylcarbonyl, alkoxycarbonylalkylcarbonyl, alkoxycarbonylcarbonyl, amino acid residue, and alkylcarbonylaminoalkylcarbonyl;

provided A^{13} is not tetrazolium, or pyridinium; and further provided A^{13} is not indanone when R^{212} is alkyl or carboxyalkyl; further provided A^{13} is not thienyl, when R^{210} is 4-fluorophenyl, when R^{211} is hydrido, and when R^{212} is methyl or acyl; and

R^{213} is hydrido;

or a pharmaceutically-acceptable salt thereof.

[0144] Specific non-limiting examples of substituted sulfonamide prodrugs of Cox-2 inhibitors disclosed in U.S. Patent No. 6,436,967 that are useful in the present invention include:

N-[[4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]phen yl]sulfonyl]propanamide;
N-[[4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]phen yl]sulfonyl]butanamide;
N-[[4-[1,5-dimethyl)-3-phenyl-1H-pyrazol-4-yl]phenyl]sulfonyl]acetamide;
N-[[4-(2-(3-pyridinyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)phenyl]sulfonyl]acetamide;
N-[[4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]butanamide;
N-[[4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]butanamide;
N-[[4-[2-(3-chloro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-[3-(3-fluorophenyl)-5-methylisoxazol-4-yl]phenyl]sulfonyl]acetamide;
2-methyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl]phenyl]sulfonyl]propanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]benzamide;
2,2-dimethyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide;
N-[[4-5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]butanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]pentanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]hexanamide;
3-methoxy-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide ;
2-ethoxy-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;
N-[[4-[5-methyl-3-phenylisoxazol-4-yl]phenyl]sulfonyl]acetamide;

N-[[4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H pyrazol-1-yl]phenyl]sulfonyl]propanamide;
N-[[4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]butanamide;
N-[[4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-[3-(difluoromethyl)-6-fluoro-1,5-dihydro-7-methoxy-[2]benzothiopyrano [4,3-c]pyrazol-1-yl)phenyl]sulfonyl]acetamide;
N-[[4-[6-fluoro-1,5-dihydro-7-methoxy-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-(2-methyl-4-phenyloxazol-5-yl)phenyl]sulfonyl]acetamide;
methyl[[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]amino]oxoacetate;
2-methoxy-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;
N-[[4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]propanamide;
N-[[4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]butanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]formamide;
1,1-dimethylethyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]carbamate;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]glycine;
2-amino-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;
2-(acetylamino)-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;
methyl 4-[[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]amino]-4-oxobutanoate;
methyl N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]carbamate;
N-acetyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]glycine, ethyl ester;

N-[[4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl]sulfonyl]acetamide;
methyl 3-[[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]amino]-3-oxopropanoate;
4-[5-(3-bromo-5-fluoro-4-methoxyphenyl)-2-(trifluoromethyl)oxazol-4-yl]-N-methylbenezenesulfonamide;
N-(1,1-dimethylethyl)-4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide;
4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-N-methylbenzenesulfonamide;
N-methyl-4-(5-methyl-3-phenylisoxazol-4-yl)benezenesulfonamide;
N-[[4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]acetamide:
N-[[4-[5-(acetoxymethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]acetamide;
N-[[4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl)phenyl]sulfonyl]acetamide;
4-[2-(4-fluorophenyl)-1H-pyrrol-1-yl]-N-methylbenzenesulfonamide;
N-[[4-(3,4-dimethyl-1-phenyl-1H-pyrazol-5-yl]phenyl]sulfonyl]propanamide;
N-[[4-[2-(2-methylpyridin-3-yl)-4-trifluoromethylimidazol-1-yl]phenyl]sulfonyl]propanamide;
4-[2-(4-fluorophenyl)cyclopenten-1-yl]-N-methylbenezenesulfonamide; and
N-[[4-(3-phenyl-2,3-dihydro-2-oxofuran-4-yl)phenyl]sulfonyl]propanamide.

[0145] Those prodrugs disclosed in U.S. Patent No. 6,613,790 have the general formula shown above in formula **XXXXII** wherein:

A^{13} is a pyrazole group optionally substituted at a substitutable position with one or more radicals independently selected at each occurrence from the group consisting of alkylcarbonyl, formyl, halo, alkyl, haloalkyl, oxo, cyano, intro, carboxyl, alkoxy, aminocarbonyl, alkoxycarbonyl, carboxyalkyl, cyanoalkyl, hydroxyalkyl, haloalkylsulonyloxy, alkoxyalkyloxyalkyl, carboxyalkoxyalkyl, alkenyl, alkynyl, alkylthio, alkylthioalkyl, alkoxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkylaminocarbonyl, alkylaminocarbonylalkyl,

alkylamino, aminoalkyl, alkylaminoalkyl, alkylsutfinyl, alkylsulfonyl, aminosulfonyl, and alkylaminosulfonyl;

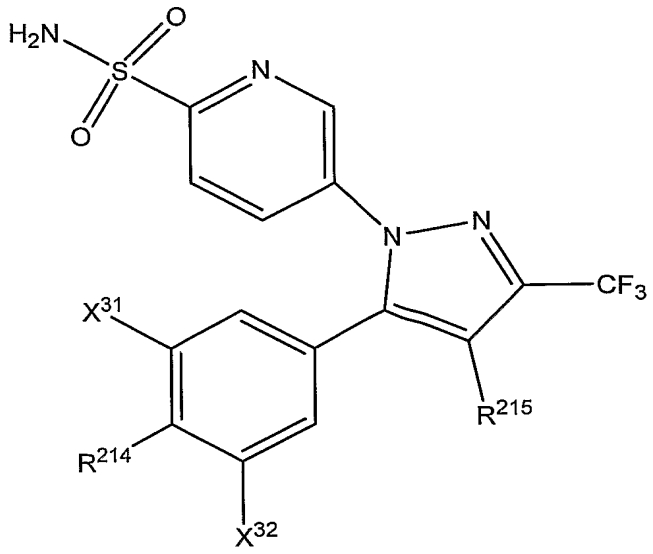
R^{210} is a phenyl group optionally substituted at a substitutable position with one or more radicals independently selected at each occurrence from the group consisting of alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy, and alkylthio;

R^{211} and R^{212} are independently selected from the group consisting of hydroxyalkyl and hydrido but at least one of R^{211} and R^{212} is other than hydrido; and

R^{213} is selected from the group consisting of hydrido and fluoro.

[0146] Examples of prodrug compounds disclosed in U.S. 6,613,790 that are useful as Cox-2 inhibitors of the present invention include, but are not limited to, N-(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, N,N-bis(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyraz ol-1-yl]benzenesulfonamide, or pharmaceuticaly-acceptable salts thereof.

[0147] Cox-2 selective inhibitors such as sulfamoylheleroaryl pyrazole compounds that are described in U.S. Patent No. 6,583,321 may serve as Cox-2 inhibitors of the present invention. Such sulfamoylheleroaryl pyrazole compounds have the formula shown below in formula **XXXXIII**:



XXXXIII

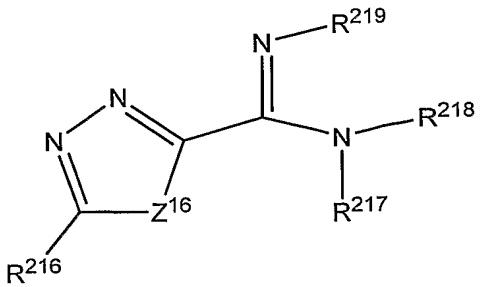
wherein:

R^{214} is furyl, thiazolyl or oxazolyl;

R^{215} is hydrogen, fluoro or ethyl; and

X^{31} and X^{32} are independently hydrogen or chloro.

[0148] Heteroaryl substituted amidinyl and imidazolyl compounds such as those described in U.S. Patent No. 6,555,563 are useful as Cox-2 selective inhibitors of the present invention. Such heteroaryl substituted amidinyl and imidazolyl compounds have the formula shown below in formula **XXXXIV**:



XXXXIV

wherein:

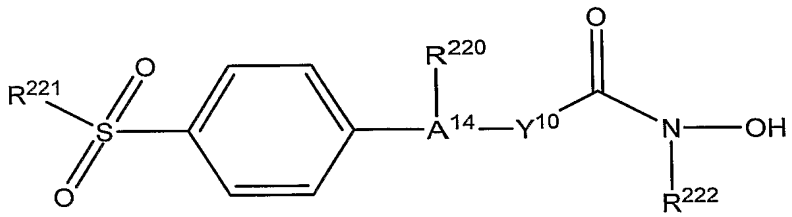
Z^{16} is O or S,

R^{216} is optionally substituted aryl,

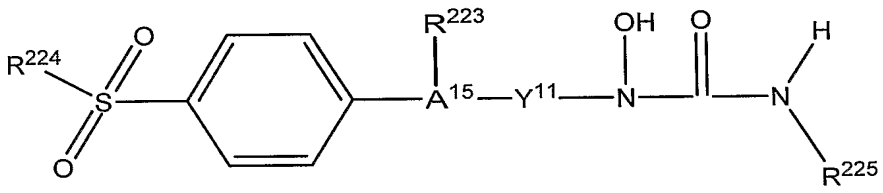
R^{217} is aryl optionally substituted with aminosulfonyl, and

R^{218} and R^{219} cooperate to form an optionally substituted 5-membered ring.

[0149] Materials that can serve as Cox-2 selective inhibitors of the present invention include substituted hydroxamic acid derivatives that are described in U.S. Patent Nos. 6,432,999, 6,512,121, and 6,515,014. These compounds also act as inhibitors of the lipoxygenase-5 enzyme. Such substituted hydroxamic acid derivatives have the general formulas shown below in formulas **XXXXV** and **XXXXVI**:



XXXXV



XXXXVI

[0150] Pyrazole substituted hydroxamic acid derivatives described in U.S. Patent No. 6,432,999 have the formula shown above in formula **XXXXV**, wherein:

A^{14} is pyrazolyl optionally substituted with a substituent selected from acyl, halo, hydroxyl, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y^{10} is selected from lower alkenylene and lower alkynylene;

R^{220} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{220} is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino,

phenylmino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{221} is selected from lower alkyl and amino; and

R^{222} is selected from hydrido, lower alkyl, phenyl, 5- and 6-membered heterocyclo and lower cycloalkyl; or a pharmaceutically-acceptable salt thereof.

[0151] Pyrazole substituted hydroxamic acid derivatives described in U.S. Patent No. 6,432,999 may also have the formula shown above in formula **XXXXVI**, wherein:

A^{15} is pyrazolyl optionally substituted with a substituent selected from acyl, halo, hydroxyl, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y^{11} is selected from lower alkylene, lower alkenylene and lower alkynylene;

R^{223} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{223} is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylmino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{224} is selected from lower alkyl and amino; and

R^{225} is selected from hydrido, lower alkyl;

or a pharmaceutically-acceptable salt thereof.

[0152] Heterocyclo substituted hydroxamic acid derivatives described in U.S. Patent No. 6,512,121 have the formula shown above in formula **XXXXV**, wherein:

A^{14} is a ring substiuent selected from oxazolyl, furyl, pyrrolyl, thiazolyl, imidazolyl, isochiazolyl, isoxazolyl, cyclopentenyl, phenyl, and pyridyl; wherein A^{14} is optionally substituted with a substituent selected

from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y^{10} is lower alkylene, lower alkenylene, and lower alkynylene;

R^{220} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{220} is otionallv substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{221} is selected from lower alkyl and amino; and

R^{222} is selected from hydrido, lower alkyl, phenyl, 5- and 6-membered heterocyclo and lower cycloalkyl; or a pharmaceutically-acceptable salt thereof.

[0153] Heterocyclo substituted hydroxamic acid derivatives described in U.S. Patent No. 6,512,121 may also have the formula shown above in formula **XXXXVI**, wherein:

A^{15} is a ring substituent selected from oxazolyl, furyl, pyrrolyl, thiazolyl, imidazolyl, isothiazolyl, isoxazolyl, cyclopentenyl, phenyl, and pyridyl; wherein A is optionally substituted with a substituent selected from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarboryl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y^{11} is selected from lower alkyl, lower alkenyl and lower alkynyl;

R^{223} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{223} is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino,

phenylamino, nitto, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{224} is selected from lower alkyl and amino; and

R^{225} is selected from hydrido and alkyl; or a pharmaceutically-acceptable salt thereof.

[0154] Thiophene substituted hydroxamic acid derivatives described in U.S. Patent No. 6,515,014 have the formula shown above in formula **XXXXV**, wherein:

A^{14} is thienyl optionally substituted with a substituent selected from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y^{10} is ethylene, isopropylene, propylene, butylene, lower alkenylene, and lower alkynylene;

R^{220} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{220} is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{221} is selected from lower alkyl and amino; and

R^{222} is selected from hydrido, lower alkyl, phenyl, 5- and 6-membered heterocyclo and lower cycloalkyl; or a pharmaceutically-acceptable salt thereof.

[0155] Thiophene substituted hydroxamic acid derivatives described in U.S. Patent No. 6,515,014 may also have the formula shown above in formula **XXXXV**, wherein:

A^{15} is thienyl optionally substituted with a substituent selected from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl,

lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

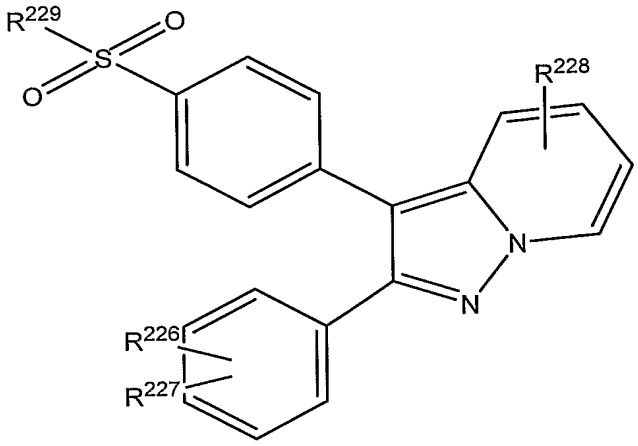
Y^{11} is selected from lower alkyl, lower alkenyl and lower alkynyl;

R^{223} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{223} is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{224} is selected from lower alkyl and amino; and

R^{225} is selected from hydrido and alkyl; or a pharmaceutically-acceptable salt thereof.

[0156] Compounds that are useful as Cox-2 selective inhibitors of the present invention include pyrazolopyridine compounds that are described in U.S. Patent No. 6,498,166. Such pyrazolopyridine compounds have the formula shown below in formula **XXXXVII**:



XXXXVII

wherein:

R^{226} and R^{227} are independently selected from the group consisting of H, halogen, C_1 –C_6 alkyl, C_1 –C_6 alkoxy, and C_1 –C_6 alkoxy substituted by one or more fluorine atoms;

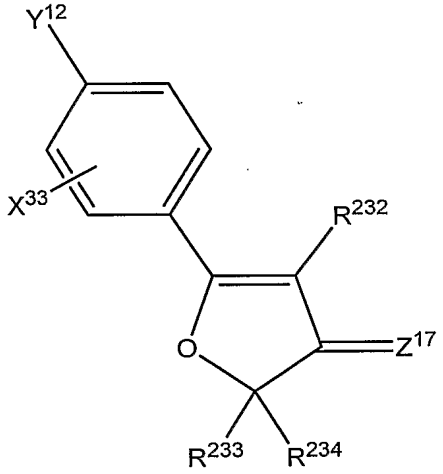
R^{228} is halogen, CN, CON R^{230} R^{231}, CO_2 H, CO_2 C_1 –C_6 alkyl, or $NHSO_2R^{230}$;

R^{229} is C_1 –C_6 alkyl or NH_2 ; and

R^{225} and R^{225} are independently selected from the group consisting of H, C_1 –C_6 alkyl, phenyl, phenyl substituted by one or more atoms or groups selected from the group consisting of halogen, C_1 –C_6 alkyl, C_1 –C_6 alkoxy, and C_1 –C_6 alkoxy substituted by one or more fluorine atoms,

or a pharmaceutically acceptable salt, solvate, ester, or salt or solvate of such ester thereof.

[0157] Materials that are useful as Cox-2 selective inhibitors of the present invention include 4,5-diaryl-3(2H)-furanone derivatives that are described in U.S. Patent No. 6,492,416. Such 4,5-diaryl-3(2H)-furanone derivatives have the formula shown below in formula **XXXXVIII**:



XXXXVIII

wherein:

X^{33} represents halo, hydrido, or alkyl;

Y^{12} represents alkylsulfonyl, aminosulfonyl, alkylsulfinyl, (N-acylamino)-sulfonyl, (N-alkylamino)sulfonyl, or alkylthio;

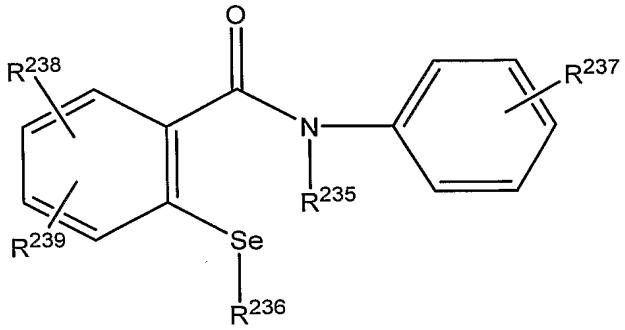
Z^{17} represents oxygen or sulfur atom;

R^{233} and R^{234} are selected independently from lower alkyl radicals; and

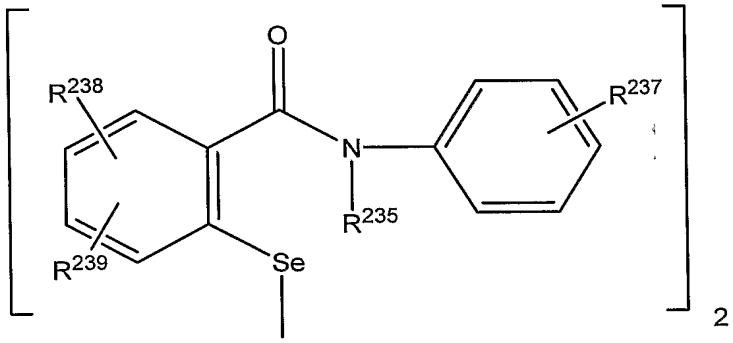
R^{232} represents a substituted or non-substituted aromatic group of 5 to 10 atoms;

or a pharmaceutically-acceptable salt thereof.

[0158] Cox-2 selective inhibitors that can be used in the present invention include 2-phenyl-1,2-benzisoselenazol-3(2H)-one derivatives and 2-phenylcarbomyl-phenylselenyl derivatives that are described in U.S. Patent No. 6,492,416. Such 2-phenyl-1,2-benzisoselenazol-3(2H)-one derivatives and 2-phenylcarbomyl-phenylselenyl derivatives have the formulas shown below in formulas **XXXXIX** or **XXXXIX'**:



XXXXIX



XXXXIX'

wherein:

R^{235} is a hydrogen atom or an alkyl group having 1-3 carbon atoms;

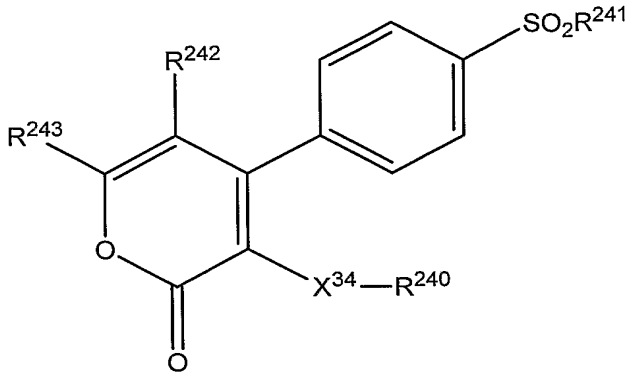
R^{236} is a hydrogen atom, a hydroxyl group, an organothiol group that is bound to the selenium atom by its sulfur atom, or R^{235} and R^{236} are joined to each other by a single bond;

R^{237} is a hydrogen atom, a halogen atom, an alkyl group having 1-3 carbon atoms, an alkoxyl group having 1-3 carbon atoms, a trifluoromethyl group, or a nitro group;

R^{238} and R^{239} are identical to or different from each other, and each is a hydrogen atom, a halogen atom, an alkoxyl group having 1-4 carbon atoms, a trifluoromethyl group, or R^{238} and R^{239} are joined to each other to form a methylenedioxy group,

a salt thereof, or a hydrate thereof.

[0159] Pyrones such as those disclosed in U.S. Patent No. 6,465,509 are also useful as Cox-2 inhibitors of the present invention. These pyrone compounds have the general formula shown below in formula **XXXXX:**



XXXXX

wherein:

X^{34} is selected from the group consisting of

(a) a bond,

(b) --$(CH_2)_m$ --, wherein m 1 or 2,

(c) --C(O)--,

(d) --O--,

(e) --S--, and

(f) --$N(R^{244})$--;

R^{240} is selected from the group consisting of

(a) C_1 –C_{10} alkyl, optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxy, halo, C_1 –C_{10} alkoxy, C_1 –C_{10} alkylthio, and CN,

(b) phenyl or naphthyl, and

(c) heteroaryl, which is comprised of a monocyclic aromatic ring of 5 atoms having one hetero atom which is S, O or N, and optionally 1, 2, or 3 additional N atoms; or

a monocyclic ring of 6 atoms having one hetero atom which is N, and optionally 1, 2, or 3 additional N atoms, wherein groups (b) and (c)

above are each optionally substituted with 1-3 substituents independently selected from the group consisting of halo, C_1 –C_{10} alkoxy, C_1 –C_{10} alkylthio, CN, C_1 –C_{10} alkyl, optionally substituted to its maximum with halo, and N_3 ;

R^{241} is selected from the group consisting of

(a) C_1 –C_6 alkyl, optionally substituted to its maximum with halo,

(b) NH_2, and

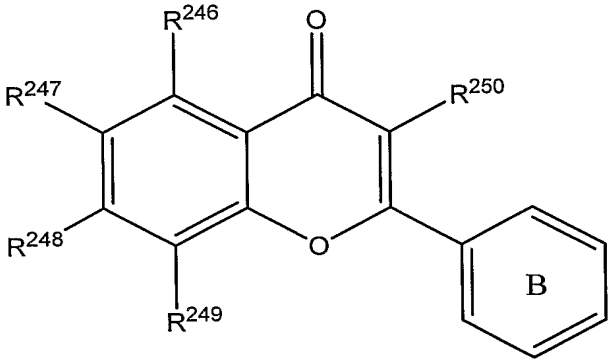
(c) $NHC(O)C_1$ –C_{10} alkyl, optionally substituted to its maximum with halo;

R^{242} and R^{243} are each independently selected from the group consisting of hydrogen, halo, and C_1 –C_6 alkyl, optionally substituted to its maximum with halo; and

R^{244} is selected from the group consisting of hydrogen and C_1 –C_6 alkyl, optionally substituted to its maximum with halo.

[0160] Examples of pyrone compounds that are useful as Cox-2 selective inhibitors of the present invention include, but are not limited to:
4-(4-Methylsulfonyl)phenyl-3-phenyl-pyran-2-one,
3-(4-Fluorophenyl)-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one,
3-(3-Fluorophenyl)-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one,
6-Methyl-4-(4-methylsulfonyl)phenyl-3-phenyl-pyran-2-one,
6-Difluoromethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-pyran-2-one,
6-Fluoromethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-pyran-2-one,
6-Methyl-4-(4-methylsulfonyl)phenyl-3-phenylthio-pyran-2-one,
6-Methyl-4-(4-methylsulfonyl)phenyl-3-phenoxy-pyran-2-one,
6-Methyl-4-(4-methylsulfonyl)phenyl-3-pyridin-3-yl-pyran-2-one,
3-Isopropylthio-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one,
4-(4-Methylsulfonyl)phenyl)-3-phenylthio-6-trifluoromethyl-pyran-2-one,
3-Isopropylthio-4-(4-methylsulfonyl)phenyl-6-trifluoromethyl-pyran-2-one,
4-(4-Methylsulfonyl)phenyl-3-phenyl-6-(2,2,2-trifluoroethyl)-pyran-2-one,
and
3-(3-Hydroxy-3-methylbutyl)-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one.

[0161] Organically synthesized or purified from plant sources, free-B-ring flavanoids such as those described in U.S. Published Application No. 2003/0165588, are useful as Cox-2 selective inhibitors of the present invention. Such free-B-ring flavanoids have the general structure shown in formula **XXXXXI**:



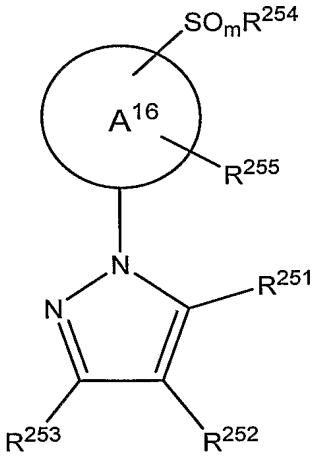
XXXXXI

wherein:

R^{246}, R^{247}, R^{248}, R^{249}, and R^{250} are independently selected from the group consisting of --H, --OH, --SH, --OR, --SR, $--NH_2$, $--NHR^{245}$, $--N(R^{245})_2$,

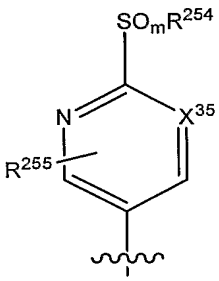
$--N(R^{245})_3{}^{+}X^{35-}$, a carbon, oxygen, nitrogen or sulfur, glycoside of a single or a combination of multiple sugars including, aldopentoses, methyl-aldopentose, aldohexoses, ketohexose and their chemical derivatives thereof; wherein R^{245} is an alkyl group having between 1-10 carbon atoms; and X^{35} is selected from the group of pharmaceutically acceptable counter anions including, hydroxyl, chloride, iodide, sulfate, phosphate, acetate, fluoride and carbonate.

[0162] Heterocyclo-alkylsulfonyl pyrazoles such as those described in European Patent Application No. EP 1312367 are useful as Cox-2 selective inhibitors of the present invention. Such heterocyclo-alkylsulfonyl pyrazoles have the general formula shown below in formula **XXXXXII**:



XXXXXII

or a pharmaceutically acceptable salt thereof, wherein the ring of the formula (R^{255})-A-(SO_mR^{254}) is selected from the group consisting of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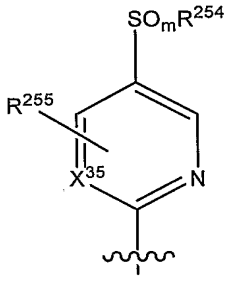
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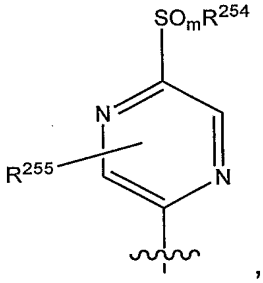
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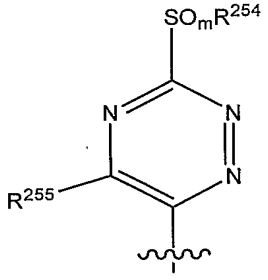
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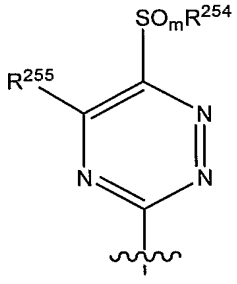
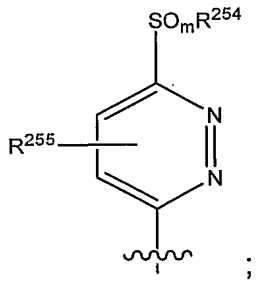

, and

;

m is 0, 1 or 2;

X^{35} is $>CR^{255}$ or >N;

R^{251} is a radical selected from the group consisting of H, NO_2, CN, (C_1-C_6)alkyl, (C_1-C_6)alkyl-SO_2-, (C_6-C_{10})aryl-SO_2-, H-(C=O)-, (C_1-C_6)alkyl-(C=O)-, (C_1-C_6)alkyl-)-(C=O)-, (C_1-C_9)heteroaryl-(C=O)-, (C_1-C_9)heterocyclyl-(C=O)-, H_2N-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, [$(C_1$ –

C_6)alkyl]$_2$-N-(C=O)-, [(C_6 –C_{10})aryl]$_2$-NH-(C=O)-, [(C_1 –C_6)alkyl]-[((C_6 – C_{10})aryl-N]-(C=O)-, HO-NH-(C=O)-, and (C_1 –C_6)alkyl-O-NH-(C=O)-;

R^{252} is a radical selected from the group consisting of H, -NO_2, -CN, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_7)cycloalkyl, (C_6-C_{10})aryl, (C_1-C_9)heteroaryl, (C_1-C_9)heterocyclyl, (C_1-C_6)alkyl-O-, (C_3-C_7)cycloalkyl-O-, (C_6-C_{10})aryl-O-, (C_1 -C_9)heteroaryl-O-, (C_6 -C_9)heterocyclyl-O-, H-(C=O)-, (C_1-C_6)alkyl-(C=O)-, (C_3-C_7)cycloalkyl-(C=O)-, (C_6-C_{10})aryl-(C=O)-, (C_1-C_9)heteroaryl-(C=O)-, (C_1-C_9)heterocyclyl-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, (C_3-C_7)cycloalkyl-O-(C=O)-, (C_6-C_{10})aryl-O-(C=O)-, (C_1-C_9)heteroaryl-O-(C=O)-, (C_1-C_9)heterocyclyl-O-(C=O)-, (C_1-C_6)alkyl-(C=O)-O-, (C_3-C_7)cycloalkyl-(C=O)-O-, (C_6-C_{10})aryl-(C=O)-O-, (C_1-C_9)heteroaryl-(C=O)-O-, (C_1-C_9)heterocyclyl-(C=O)-O-, (C_1-C_6)alkyl-(C=O)-NH-, (C_3-C_7)cycloalkyl-(C=0)-NH-, (C_6-C_{10}aryl-(C=O)-NH-. (C_1-C_9)heteroaryl-(C=O)-NH-, (C_1-C_9)heterocyclyl-(C=O)-NH-, (C_1-C_6)alkyl-O-(C=O)-NH-, (C_1-C_6)alkyl-NH, [(C_1-C_6)alkyl]$_2$-N-, (C_3-C_7)cycloalkyl-NH-. [(C_3-C_7)cycloalkyl]$_2$-N-, [(C_6-C_{10})aryl]-NH-, [(C_6-$C_{1\,0}$)aryl]$_2$-N-, [(C_1 –C_6)alkyl]-[((C_6-C_{10})aryl)-N]-, [(C_1 -C_9)heteroaryl]-NH-, [(C_1-C_9)heteroaryl]$_2$-N-, [(C_1-C_9)heterocycly]-NH-, [(C_1-C_9)heterocyclyl]$_2$-N-, H_2N-(C=O)-, HO-NH-(C=O)-, (C_1-C_6)alkyl-O-NH-(C=O)-, [(C_1-C_6)alkyl]-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, [(C_3-C_7)cycloalkyl]-NH-(C=O)-, [(C_3-C_7)cycloalkyl]$_2$-N-(C=O)-, [(C_6-C_{10})aryl]-NH-(C=O)-, [(C_6-C_{10}aryl]$_2$-N-(C=O)-, [(C_1-$C_{\,6}$)alkyl]-[((C_6-C_{10})aryl)-N]-(C=O)-, [(C_1-C_9)heteroaryl]-NH-(C=O)-, [(C_1-C_9)heferoaryl]$_2$-N-(O=O)-, [(C_1-C_9)heterocyclyl]-NH-(C=O)-, (C_1–C_6)alkyl-S- and (C_1-C_6)alkyl optionally substituted by one -OH substituent or by one to four fluoro substituents;

R^{253} is a saturated (3- to 4-membered)-heterocyclyl ring radical; or a saturated, partially saturated or aromatic (7- to 9-membered)-heterocyclyl ring radical;

wherein said saturated (3- to 4-membered)-heterocyclyl ring radical orsaid saturated, partially saturated or aromatic (7- to 9-membered)-heterocyclyl ring radical; may optionally contain one to four ring heteroatoms independently selected Irom the groups consisting of -N=, -NH-, -O-, and -S-;

wherein said saturated (3- to 4-membered)-heterooyclyl ring radical; or said saturated, partially saturated or aromatic (7- to 9-membered)-heterocyclyl ring radical; may optionally be substituted on any ring carbon atom by one to three substituents per ring independently selected from the group consisting of halo, -OH, -CN, -NO_2, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_7)cycloalkyl, (C_6-C_{10})aryl, (C_2-C_9)hetorocyclyl, (C_1 –C_6)alkyl-O-, H-(C=0)-, (C_1-C_6)alkyl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, -NH_2, (C_1-C_6)alkyl-NH-, [(C_1-C_6) alkyl]$_2$-N-, (C_3-C_7)cycloalkyl-NH-, (C_6-C_{10})aryl-NH-, [(C_1-C_6)alkyl]-[((C_6-C_{10})aryl)-N]-, (C_1-C_9)heteroaryl-NH-, H_2N-(C=O)-[(C_1-C_6)alkyl]-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, [(C_6-C_{10})aryl]-NH-(C=O)-, [(C_1-C_6)alkyl]-[((C_6-C_{10})aryl)-N]-(C=O)-, (C_1-C_6)alkyl-O-NH-(C=O)-, (C_1-C_6)alkyl-(C=O)-HN-, (C_1-C_6)alkyl-(C=O)-[(C_1-C_6)alkyl-N]-, -SH, (C_1-C_6)alkyl-S-, (C_1-C_6)alkyl-(S=0)-, (C_1-C_6)alkyl-SO_2- and (C_1-C_6)alkyl optionally substituted with one to fourfluoro moieties;

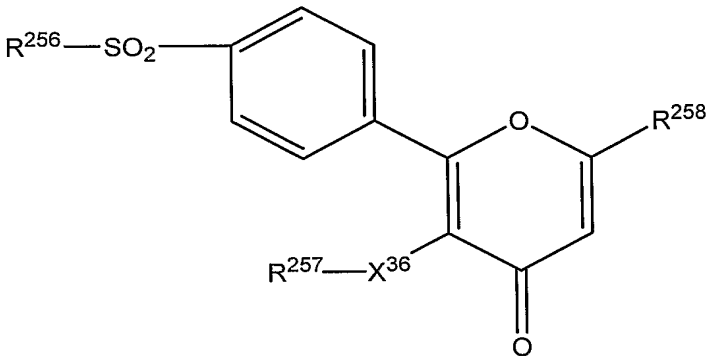
wherein said saturated (3- to 4-membered)-heterocyclyl ring radical; or said saturated, partially saturated or aromatic (7- to 9-membered)-heterocyclyl ring radical; may also optionally be substituted on any ring nitrogen atom by one to three substituents per ring independently selected from the group consisting of (C_3-C_7)cyoloalkyl, (C_6-C_{10})aryl, (C_2-C_9)heterocyclyl, H-(C=O)-, (C_1-C_6)alkyl-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N-(C=O)-, [(C_1-C_6)alkyl]-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, [(C_6-C_{10})aryl]-NH-(C=O)-, [(C_1-C_6)alkyl]-[((C_6-C_{10})aryl)-N]-(C=O)-, (C_1 –C_6)alkyl-O-NH-(C=O)-, and (C_1-C_6)alkyl optionally substituted with one to four fluoro moieties;

R^{254} is an (C_1-C_6)alkyl radical optionally substituted by one to four fluoro substituents; and

R^{255} is a radical selected from the group consisting of H, halo, -OH, (C_1-C_6)alkyl-O-, (C_2-C_6)alkenyl, (C_2-C_6) alkynyl, (C_3-C_7)cycloalkyl, -CN, H-(C=O)-, (C_1-C_6)alkyl-(C=O)-, (C_1-C_6)alkyl-(C=O)-O-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, (C_1-C_6)alkyl-NH-. [(C_1-C_6)alkyl]$_2$-N-, (C_3-C_7)cycloalkyl-NH-, (C_6-C_{10})aryl-NH-, [(C_1-C_6)alkyl]-[((C_6-C_{10})aryl)-N]-,

$(C_1$-$C_9)$heteroaryl-NH-, H_2N-(C=O)-, $(C_1$-$C_6)$alkyl-NH-(C=O)-. $[(C_1$-$C_6)$alkyl$]_2$-N-(C=O)-, $(C_6$-$C_{10})$aryl-(C=O)-, $[(C_1$-$C_6)$alkyl]-[$(C_6$-$C_{10})$aryl)-N]-(C=O)-, $(C_1$-$C_6)$alkyl-O-NH-(C=O)-, $(C_1$-$C_6)$alkyl-S-, and $(C_1$-$C_6)$alkyl optionally substituted by one to four fluoro substituents.

[0163] 2-phenylpyran-4-one derivatives such as those described in U.S. Patent No. 6,518,303 are also useful as Cox-2 selective inhibitors of the present invention. Such 2-phenylpyran-4-one derivatives have the general formula shown below in formula **XXXXXIII**:



XXXXXIII

wherein:

R^{256} represents an alkyl or $-NR^{259}R^{260}$ group, wherein R^{259} and R^{260} each independently represents a hydrogen atom or an alkyl group;

R^{257} represents an alkyl, C_3-C_7 cycloalkyl, naphthyl, tetrahydronaphthyl or indanyl group, or a phenyl group which may be unsubstituted or substituted by one or more halogen atoms or alkyl, trifluoromethyl, hydroxy, alkoxy, methylthio, amino, mono- or dialkylamino, hydroxyalkyl or hydroxycarbonyl groups;

R^{258} represents a methyl, hydroxymethyl, alkoxymethyl, C_3-C_7 cycloalkoxymethyl, benzyloxymethyl, hydroxycarbonyl, nitrile, trifluoromethyl or difluoromethyl group or a CH_2 -- R^{261} group wherein R^{261} represents an alkyl group; and

X^{36} represents a single bond, an oxygen atom, a sulfur atom or a methylene group;

or a pharmaceutically acceptable salt thereof.

[0164] Examples of 2-phenylpyran-4-one derivatives useful in the present invention include, but are not limited to:
3-(4-fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2-fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-chlorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-bromophenyl)-2-(4-methylsulfonylphenyl)-6-methylpyran-4-one,
3-(2,4-difluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(3,4-dichlorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(3-chloro-4-methylphenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one ,
2-(4-methanesulfonylphenyl)-6-methyl-3-phenoxypyran-4-one,
3-(4-fluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2-fluorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-chlorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2-chlorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-bromophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
2-(4-methanesulfonylphenyl)-6-methyl-3-(4-methylphenoxy)pyran-4-one,
3-(2,4-difluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2,5-difluorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-chlorophenyl)-2-(4-methanesulfonylphenyl)-6-methoxymethylpyran-4-one,
3-(4-chlorophenyl)-6-difluoromethyl-2-(4-methanesulfonylphenyl)pyran-4-one,
and pharmaceutically acceptable salts thereof.

[0165] Cox-2 selective inhibitors that are useful in the subject method and compositions can include the compounds that are described in U.S. Patent No. 6,472,416 (sulfonylphenylpyrazoles); U.S. Patent No. 6,451,794 (2,3-diaryl-pyrazolo[1,5-b]pyridazines); U.S. Patent Nos. 6,169,188, 6,020,343, and 5,981,576 ((methylsulfonyl)phenyl furanones); U.S. Patent No. 6,222,048 (diaryl-2-(5H)-furanones); U.S. Patent No. 6,057,319 (3,4-diaryl-2-hydroxy-2,5-dihydrofurans); U.S. Patent No.

6,046,236 (carbocyclic sulfonamides); U.S. Patent Nos. 6,002,014 and 5,945,539 (oxazole derivatives); and U.S. Patent Nos. 6,359,182 and 6,538,116 (C-nitroso compounds).

[0166] Examples of specific compounds that are useful as Cox-2 selective inhibitors include, without limitation:

a1) 8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a)pyridine;

a2) 5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone;

a3) 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;

a4) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole;

a5) 4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a6) 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a7) 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;

a8) 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a9) 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a10) 4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

b1) 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;

b2) 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide

b3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b4) 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b5) 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b6) 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b7) 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b8) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b9) 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b10) 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c1) 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

c2) 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c3) 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c4) 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c6) 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

c7) 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c8) 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c9) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

c10) 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d1) 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;

d2) 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d3) 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d4) 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d5) 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d6) 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d7) 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

d8) 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

d9) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;

d10) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

e1) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;

e2) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;

e3) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;

e4) 2-[(3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;

e5) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

e6) 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene;

e7) 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide;

e8) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;

e9) 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide;

e10) 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;

f1) 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;

f2) 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile;

f3) 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f4) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f5) 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f6) 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f7) 2-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f8) 2-methyl-4-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f9) 2-methyl-6-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f10) 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g1) 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;

g2) 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g3) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;

g4) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;

g5) 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;

g6) 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazole;

g7) 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;

g8) 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;

g9) 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g10) 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;

h1) 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

h2) 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;

h3) 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h4) 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;

h5) 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h6) 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h7) 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h8) 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;

h9) 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl]benzenesulfonamide;

i1) N-phenyl-[4-(4-luorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;

i2) ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;

i3) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;

i4) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;

i5) 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;

i6) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole;

i7) 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;

i8) 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

i9) 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

i10) 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine;

j1) 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

j2) 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;

j3) 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;

j4) 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;

j5) 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;

j6) 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

j7) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

j8) 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;

j9) 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

j10) 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k1) 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k2) 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k3) 1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k4) 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k5) 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k6) 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

k7) 1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k8) 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

k9) 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

k10) 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;

l1) 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l2) 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l3) 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide;

l4) 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l5) 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

l6) 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide;

l7) ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl) phenyl]oxazol-2-yl]-2-benzyl-acetate;

l8) 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;

l9) 2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;

l10) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;

m1) 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole; and

m2) 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;

m3) 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m4) 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m5) 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m6) 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m7) 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m8) 2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid;

m9) 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m10) 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n1) 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n2) 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n3) 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n4) 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n5) 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n6) 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n7) 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n8) 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n9) 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n10) 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o1) 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o2) 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o3) 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o4) 2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid;

o5) 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o6) 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o7) 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o8) 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o9) 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o10) 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p1) 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p2) 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p3) 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p4) 6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p5) 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p6) 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p7) 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p8) 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p9) 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p10) 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q1) 8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q2) 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q3) 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q4) 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q5) 6,8-dichloro-(*S*)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q6) 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q7) 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q8) 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q9) 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q10) 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid;

r1) 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methyl-sulphonyl-2(5H)-fluranone;

r2) 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;

r3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r4) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r6) 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

r7) 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

r8) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

r9) 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

r10) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

s1) [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;

s2) 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide; or

s3) 4-[5-(3-fluoro-4-methoxyphenyl-2-trifluoromethyl)-4-oxazolyl]benzenesulfonamide;

or a pharmaceutically acceptable salt or prodrug thereof.

[0167] Cox-2 inhibitors that are useful in the methods and compositions of present invention can be supplied by any source as long as the Cox-2 inhibitor is pharmaceutically acceptable. Likewise, Cox-2 inhibitors that are useful in the compositions and methods of present invention can by synthesized, for example, according to the description in Example 1. Several Cox-2 inhibitors that are suitable for use with the compositions and methods of the present invention may be synthesized by the methods described in, for example, U.S. Patent No. 5,466,823 to Talley, *et al.* Cox-2 inhibitors can also be isolated and purified from natural sources. Cox-2 inhibitors should be of a quality and purity that is conventional in the trade for use in pharmaceutical products.

[0168] Preferred Cox-2 selective inhibitor compounds are those compounds selected from the group consisting of celecoxib, parecoxib, deracoxib, valdecoxib, etoricoxib, meloxicam, rofecoxib, lumiracoxib, RS 57067, T-614, BMS-347070 (Bristol Meyers Squibb, described in U.S. Patent No. 6,180,651), JTE-522 (Japan Tabacco), S-2474 (Shionogi), SVT-2016, CT-3 (Atlantic Pharmaceutical), ABT-963 (Abbott), SC-58125 (GD Searle), nimesulide, flosulide, NS-398 (Taisho Pharmaceutical), L-745337 (Merck), RWJ-63556, L-784512 (Merck), darbufelone (Pfizer), CS-502 (Sankyo), LAS-34475 (Almirall Prodesfarma), LAS-34555 (Almirall Prodesfarma), S-33516 (Servier), SD-8381 (Pharmacia, described in U.S. Patent No. 6,0340256), MK-966 (Merck), L-783003 (Merck), T-614 (Toyama), D-1376 (Chiroscience), L-748731 (Merck), CGP-28238 (Novartis), BF-389 (Biofor/Scherer), GR-253035 (Glaxo Wellcome), prodrugs of any of them, and mixtures thereof.

[0169] More preferred is that the Cox-2 selective inhibitor is selected from the group consisting of celecoxib, parecoxib, deracoxib, valdecoxib, lumiracoxib, etoricoxib, rofecoxib, prodrugs of any of them, and mixtures thereof.

[0170] Even more preferred still is that the Cox-2 selective inhibitor is celecoxib.

[0171] Cox-2 inhibitors that are useful in the methods and compositions and methods of present invention can be supplied by any source as long as the Cox-2 inhibitor is pharmaceutically acceptable. Likewise, Cox-2 inhibitors that are useful in the compositions and methods of present invention can by synthesized, for example, according to the description in Example 1. Several Cox-2 inhibitors that are suitable for use with the compositions and methods of the present invention may be synthesized by the methods described in, for example, U.S. Patent No. 5,466,823 to Talley, *et. al.*

[0172] Various classes of Cox-2 inhibitors useful in the present invention can be prepared as follows. Pyrazoles can be prepared by methods described in WO 95/15316. Pyrazoles can further be prepared by methods described in WO 95/15315. Pyrazoles can also be prepared by methods described in WO 96/03385.

[0173] Thiophene analogs useful in the present invention can be prepared by methods described in WO 95/00501. Preparation of thiophene analogs is also described in WO 94/15932.

[0174] Oxazoles useful in the present invention can be prepared by the methods described in WO 95/00501. Preparation of oxazoles is also described in WO 94/27980.

[0175] Isoxazoles useful in the present invention can be prepared by the methods described in WO 96/25405.

[0176] Imidazoles useful in the present invention can be prepared by the methods described in WO 96/03388. Preparation of imidazoles is also described in WO 96/03387.

[0177] Cyclopentene Cox-2 inhibitors useful in the present invention can be prepared by the methods described in U.S. Patent No. 5,344,991. Preparation of cyclopentene Cox-2 inhibitors is also described in WO 95/00501.

[0178] Terphenyl compounds useful in the present invention can be prepared by the methods described in WO 96/16934.

[0179] Thiazole compounds useful in the present invention can be prepared by the methods described in WO 96/03392.

[0180] Pyridine compounds useful in the present invention can be prepared by the methods described in WO 96/03392. Preparation of pyridine compounds is also described in WO 96/24585.

[0181] Benzopyranopyrazolyl compounds useful in the present invention can be prepared by the methods described in WO 96/09304.

[0182] Chromene compounds useful in the present invention can be prepared by the methods described in WO 98/47890. Preparation of chromene compounds is also described in WO 00/23433. Chromene compounds can further be prepared by the methods described in U.S. Patent No. 6,077,850. Preparation of chromene compounds is further described in U.S. Patent No. 6,034,256.

[0183] Arylpyridazinones useful in the present invention can be prepared by the methods described in WO 00/24719. Preparation of arylpyridazinones is also described in WO 99/10332. Arylpyridazinones can further be prepared by the methods described in WO 99/10331.

[0184] 5-Alkyl-2-arylaminophenylacetic acids and derivatives useful in the present invention can be prepared by the methods described in WO 99/11605.

[0185] Diarylmethylidenefuran derivative Cox-2 selective inhibitors useful in the present invention can be prepared by the methods described in U.S. Patent No. 6,180,651.

[0186] The celecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,466,823.

[0187] The valdecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,633,272.

[0188] The parecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,932,598.

[0189] The rofecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,474,995.

[0190] The deracoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,521,207.

[0191] The etoricoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in WO 98/03484.

[0192] The meloxicam used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,233,299.

[0193] The compound 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,994,381.

[0194] The compound 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone used in the compositions and methods of the present invention can be prepared in the manner set forth in WO 00/24719.

[0195] The compound 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one used in the compositions and methods of the present invention can be prepared in the manner set forth in EP 863134.

[0196] The compound 2-[(2-chloro-6-fluorophenyl)amino]-5-methyl-benzeneacetic acid used in the compositions and methods of the present invention can be prepared in the manner set forth in WO 99/11605.

[0197] The compound N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,885,367.

[0198] The compound (3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 6,180,651.

[0199] Cox-2 inhibitors can also be isolated and purified from natural sources. Cox-2 inhibitors should be of a quality and purity that is conventional in the trade for use in pharmaceutical products.

[0200] An optional component of the combination therapy embodiments of the present invention is an antidepressant agent.

[0201] As used herein, the phrase "antidepressant agent" means an agent or compound, or a combination of two or more of such agents or compounds, which treat or prevent psychiatric disorders or symptoms of a psychiatric disorder in a subject in need of such treatment.

[0202] Antidepressant agents display a wide range of chemical structures. Some of the structural classes of antidepressant agents that are encompassed by the present invention include tricyclics, tetracylics, hydrazides/hydrazines, bicyclics, benzodiazepines, and pyrrolidones.

[0203] Antidepressant agents also perform a wide range of functions within the subject's body. Some of the functional classes of antidepressant agents that are encompassed by the present invention include selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, noradrenaline reuptake inhibitors, selective serotonin and noradrenaline reuptake inhibitors, dual-action serotonin norepinephrine reuptake inhibitors, norepinephrine antagonist serotonin antagonists, selective serotonin and noradrenaline reuptake inhibitors, serotonin

antagonist and reuptake inhibitors, norepinephrine dopamine reuptake inhibitor, and serotonin reuptake accelerators.

[0204] In one embodiment, sertraline (Zoloft®), in particular, has been found to be a preferred antidepressant agent. Sertraline was initially introduced for the treatment of depression, but it is now used to treat a wide variety of psychiatric disorders. See Khouzam H., et al., Compr Ther 29(1):47-53 (2003). Sertraline acts as a selective serotonin reuptake inhibitor (SSRI) through oral administration. However, it is chemically unrelated to other SSRIs, tricyclic, tetracyclic, or other available antidepressant agents.

[0205] In another embodiment, the present invention encompasses one or more of the antidepressant agents described in Table 3 below.

Table 3: Antidepressant Agents

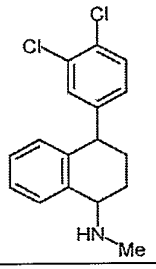
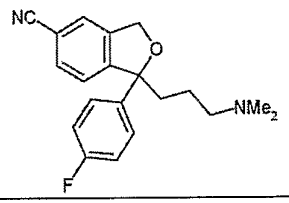
No.	Compound Name	Trade Name(s)	Drug Class	Dose	Manufacturer	Reference
1	**Sertraline HCl** (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-nanphthalenamine hydrochloride 	Zoloft® Altruline® Sercerin® Lustral®	Selective Serotonin Reuptake Inhibitor (SSRI), Bicyclic	50-200 mg/day	Pfizer Inc.	U.S. Patent No. 4,045,488 and 4,556,676 and 4,536,518.
2	**Citalopram HBr** (±)-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile HBr 	Celexa® Cipramil® Prisdal®	SSRI, bicyclic	40 mg/day	Forest Pharmaceuticals, Inc	U.S. Patent No. 4,943,590.

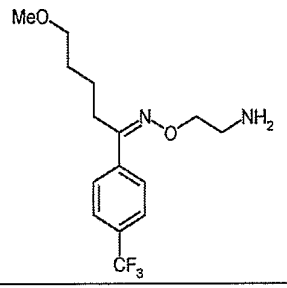
Table 3: Antidepressant Agents						
3	**Escitalopram oxalate** S-(+)-1-[3-dimethylamino)propyl]-1-(*p*-fluorophenyl)-5-phthalancarbonitrile oxalate	Lexapro®	SSRI	10-50 mg/day	Forest Pharmaceuticals, Inc	U.S. Patent No. 6,455,710
4	**Fluvoxamine** 5-methoxy-4'-(trifluoromethyl) valerophenone (E)-O-(2-aminoethyl)oxime maleate (1:1)  	Luvox® Faverin® Floxyfral®	SSRI	100-300 mg/day	Solvay Pharmaceuticals, Inc	Martin, A., *et al.*, *J Autism Dev Disorder 33(1)*:77-85 (2003).

Table 3: Antidepressant Agents

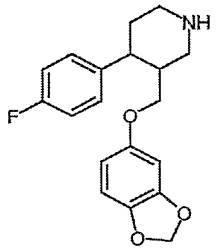
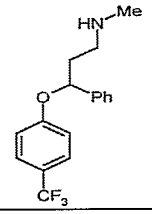
5	**Paroxetine HCl** (-) - (3S,4R)-4-[(p-fluorophenyl)-3-[(3,4-methylenedioxy) phenoxy]methyl]piperidine hydrochloride hemihydrate 	Paxil® Aropax® Seroxat® Aroxat®	SSRI, bicyclic	20-50 mg/day	GlaxoSmith Kline	U.S. Patent Nos. 2,680,743; 2,734,063; 2,904,551; and 3,024,244
6	**Fluoxetine HCl** (±)-N-methyl-3-phenyl-3-[(a,a,a-trifluoro-p-tolyl)-oxy]propylamine hydrochloride 	Prozac® Deprax® Eufor® Psiquial® Lovan®	SSRI	20-150 mg/day	Eli Lilly and Company	U.S. Patent No. 4,590,213.

Table 3: Antidepressant Agents

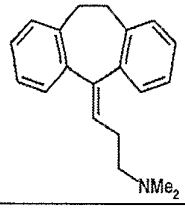
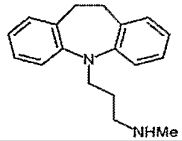
7	**Amitriptyline HCl** 3-(10,11-dihydro-5*H*-dibenzo [a,*d*] cycloheptene-5-ylidene)-*N,N*-dimethyl-1-propanamine hydrochloride 	Elavil® Endep® Sarotex® Typtanol® Typtizol®	Tricyclic	50-300 mg/day	Astrazeneca	U.S. Patent No. 4,495,281
8	**Desipramine** 5H Dibenz[b,f] azepine-5-propanamine, 10, 11-dihydro-N-methyl-. Monohydrochloride 	Norpramine® Pertofrane®	Tricyclic	100-300 mg/day		Swann, A., *et al.*, *J Clin Psychopharmacol 17(2)*:78-83 (1997).

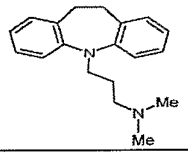
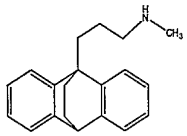
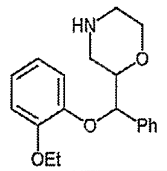
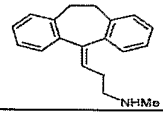
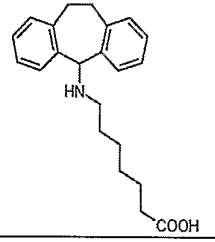
Table 3: Antidepressant Agents						
9	**Imipramine** 5-[3-(Dimethylamino)propyl]- 10,11- ihydro-5H-dibenz [b,1-azepine] Monohydrochloride 	Tofranil® Jaminine	Tricyclic	50-300 mg/day		Van Amerongen, A., *et al., J Affect Disord 72(1)*:21-31 (2002).
10	**Maprotiline** N-methyl-9,10- ethanoanthracene- 9(10H)-propanamine 	Ludiomil®	tetracyclic	25-150 mg/day	Novartis	Kudoh, A., *et* al., *Pharmacopsychiatry 36(2)*:57-60 (2003).
11	**Reboxetine** 	Edronax®, Vestra®	Noradrenaline Reuptake Inhibitor	4-12 mg/day		Montgomery, S., *et al., J Clin Psychopharmacol 23(1)*:45-50 (2003).

Table 3: Antidepressant Agents

12	**Nortriptyline** 1-Propanamine, 3-(10,11-dihydro, 5H-dibenzo [a, d] cyclohepten- 5-ylidene)-N-methyl-,hydrochloride 	Aventyl®, Pamelor® Nortilen®	Tricyclic	50-150 mg/day		Nierenberg, A., *et al.*, *J Clin Psychiatry 64(1)*:35-9 (2003).
13	**Amineptine** 7-[(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)amino]heptanoic acid 	Survector® Directim® Maneon®	Tricyclic	100-200 mg/day		Ferreri, M., *et al.*, *Int Clin Psychopharmacol 12 Suppl 3*:S39-45 (1997).
14	**Zimelidine** (Z)-3-(4-bromophenyl)-N,N-dimethyl-3-(3-pyridinyl)-2-propen-1-amine	Zelmid®		75-300 mg/day		Merck Index, 12th ed, No. 10254

Attorney Docket: 6794-197/POA
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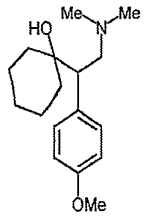
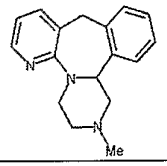
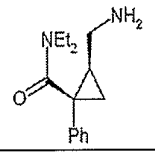
Table 3: Antidepressant Agents						
15	**Venlafaxine** (R/S)-1-[2-(dimethylamino)-1-(4 methoxyphenyl)ethyl] cyclohexanol hydrochloride or (±)-1-[a [(dimethylamino)methyl] p-methoxybenzyl] cyclohexanol hydrochloride  	Effexor® EffexorXR® Dobupal®	Dual-action serotonin norepinephrine reuptake inhibitor	75-300 mg/day		U.S. Patent Nos. 6,274,171 and 4,535,186

Table 3: Antidepressant Agents						
16	**Mirtazapine** 1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a] pyrido [2,3-c] benzazepine 	Remeron® Norset® Zipsin®	Tetracyclic	15-45 mg/day		U.S. Patent Nos. 4,062,848 and 4,515,792
17	**Milnacipran** Cis-(±)-2-(aminomethyl)-*N,N*-diethyl-1-phenylcyclopropanecarboxamide 	Ixel®	Selective serotonin and noradrenaline reuptake inhibitor (SNRI)	50-200 mg/day		Van Amerongen, A., et al., J Affect Disord 72(1):21-31 (2002).

Attorney Docket: 6794-197/POA
Client Ref.: 01430/1

Table 3: Antidepressant Agents

18	**Phenelzine** (2-phenethyl)hydrazine 	Nardil®	Monoamine oxidase inhibitor, hydrazides/hydrazines	30-90 mg/day	Parke-Davis	Swann, A,, *et al., J Clin Psychopharmacol 17(2)*:78-83 (1997).
19	**Tranylcypromine** (±)- trans -2-phenylcyclopropylamine sulfate (2:1) 	Parnate®	Monoamine oxidase inhibitor	20-120 mg/day	Smithkline Beecham	Joffe, R., *Int Clin Psychopharmacol 11(4)*:287-8 (1996).

Attorney Docket: 6794-197/POA
Client Ref.: 01430/1

Table 3: Antidepressant Agents

20	**Nefazodone** 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ether-2,4-dihydro-4-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one monohydrochloride 	Serzone® Dutonin® Nefadar®	Serotonin Antagonist and Reuptake inhibitor (SARI)	150-600 mg/day	Bristol-Myers Squibb	Grunze H, *et al.*, *Neuropsychobiology 46 Suppl 1*:31-5 (2002).

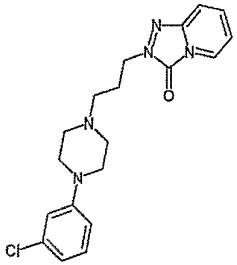
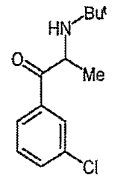
Table 3: Antidepressant Agents						
21	**Trazodone** 2-[3-{4 -(m-Chlorophenyl)-1-piperazinyl] propyl]s-triazol[4,3-a]-pyridine-3(2H)-one monohydrochloride 	Desyrel®	Serotonin Antagonist and Reputake inhibitor (SARI), bicyclic	100-600 mg/day	Apothecon, Princeton, NJ	U.S. Patent No. 4,613,600
22	**Bupropion** (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride 	Wellbutrin® Zyban®	Norepinephrine dopamine reuptake inhibitor	300-450 mg/day, 150-300 mg/day	GlaxoSmith Kline	U.S. Patent Nos. 6,391,875 and 4,347,176

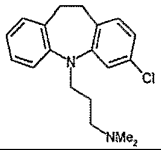
Table 3: Antidepressant Agents						
23	**Clomipramine** 3-chloro-5-[3-(dimethylamino)propyl]-10.11-dihydro-5H-dibenz[b.f]azepine monohydrochloride 	Anafranil®, Clofranil®	Tricyclic	25-2500 mg/day		Ackerman, D., *et al.*, *J Clin Psychopharmacol* *22(3)*:309-17 (2002).
24	**Tandospirone** 4,7-methano-1H-isoindole-1,3(2H)-dione, hexahydro-2›4-›-(2-pyrimidinyl)-1-piperazinyl!butyl!-(3a.alpha.,4.beta.,7.beta.,7a.alpha.)-2-hydroxy-1,2,3-propanetricarboxylate (1:1) or as N-›4-›4-(2-pyrimidinyl)-1-piperazinyl!butyl-2,3-norbornanedicarboximide					U.S. Patent Nos. 5,011,841 and 4,507,303

Table 3: Antidepressant Agents

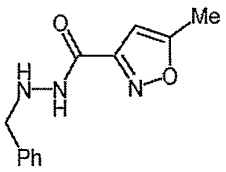
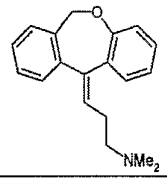
25	**Isocarboxazid** 5-methyl-3-isoxazolecarboxylic acid 2-benzylhydrazide 	Marplan®	Monoamine oxidase inhibitor	30-80 mg/day	Roche	Davidson, J., *et al.*, *Arch Gen Psychiatry 45(2)*:120-7 (1988).
26	**Lithium Carbonate** Li_2CO_3	Eskalith®, Lithobid® Lithotabs				
27	**Lithium Citrate**	Cibalith®-Sr				
28	**Doxepin** 1-Propanamine,3-dibenz[b,e] oxepin-1,1(6H) ylidene N, N-dimethyl-hydrochloride 	Adapin® Sinequan®	tricyclic	75-300 mg/day		Ayd, F., Jr., *J Clin Psychiatry 45(3 Pt 2)*:39-46 (1984).

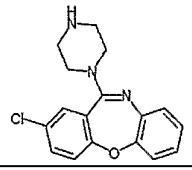
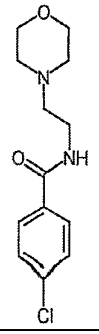
Table 3: Antidepressant Agents						
29	**Amoxapine** 2-chloro-11-(1-piperazinyldibenz-[b,f][1,4]oxapine 	Asendin® Asendas®	Tricyclic	75-400 mg/day		Schmultz, J., *et al.*, *Helv. Chim. Acta* *15*:245 (1967).
30	**Moclobemide** 4-chloro-*N*-[2-(4-morpholinyl)-ethyl}benzamide 	Manerix, Aurorix, Moclamine	Serotonin and Norepinephrine Reuptake Inhibitors (SNRI).	150-600 mg/day		Kimura, M., *et al.*, *International Clinical Psychopharmacology* *17*: 121-125 (2002).

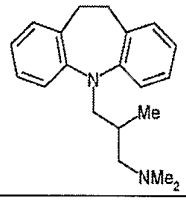
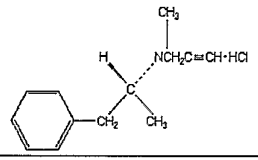
Table 3: Antidepressant Agents						
31	**Trimipramine** 5-[3-(dimethylamino)-2-methylpropyl]-10,11-dihydro-5H-dibenz[b,f]azepine 	Surmontil, Rhotrimine	Tricylic	50-300 mg/day		Berger, M.,*et al., Eur Arch Psychiatry Clin Neurosci 246(5)*:235-9 (1996).
32	**Selegiline** (-)Deprenyl, or (R)-(-)-N,2-dimethyl-N-2-propynylphenethylamine hydrochloride 	l-deprenyl, Eldepryl, Jumex, Carbex	Monoamine oxidase inhibitor	5-30 mg/day		Mann JJ, *et al.*, *Arch Gen Psychiatry 46(1)*:45-50 (1989).

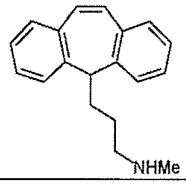
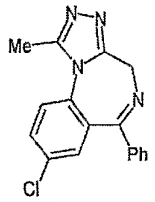
Table 3: Antidepressant Agents						
33	**Protriptyline** *N*-methyl-5H-dibenzo[a,d]cycloheptene-5-propamine  	Vivactil, Triptil	Tricylic	15-60 mg/day		U.S. Pat. Nos. 3,244,748 and 3,271,451
34	**Viloxazine** 2-[(2-ethoxyphenoxy)methyl]morpholine	Vivalan		15-30 mg/day		Merck Index, 12th ed, no 10116
35	**Alprazolam** 8-Chloro-1-methyl-6-phenyl-4H-s-triazolo [4,3-a][1,4] benzodiazepine  	Xanex, Helix	benzodiazepine	.75-10 mg/day		U.S. Patent No. 4,595,684.

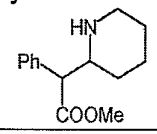
Table 3: Antidepressant Agents						
36	**Pargyline** N-methyl-N-2-propynylbenzenemethanamine	Eutonyl, Eudatine, Tenalin		90 mg/day		Merck Index, 12th ed., no 7172
37	**Dextroamphetamine** d-a-methylphenethylamine (Combination of the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextroisomer of amphetamine saccharate and 6, l-amphetamine aspartate)	Dexedrine® (Adderall®)		Up to 40 mg/day	GlaxoSmith Kline	
38	**Methylphenidate** methyl a-phenyl-2-piperi-dineeacetate hydrochloride 	Ritalin®		Up to 60 mg/day	CIBA-Geigy Corporation	Kimko, H., *et al.*, *Clin Pharmacokine 37(6)*:457-70 (1999).

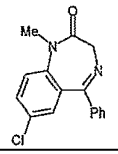
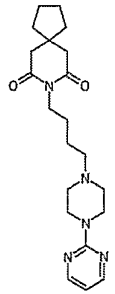
Table 3: Antidepressant Agents						
39	**Diazepam** 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one 	Valium, Dizac	benzodiazepine	10-40 mg/day	Roche	U.S. Patent No. 3,932,325.
40	**Buspirone HCl** 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl) butyl)-8-azaspiro [4,5] decane-7,9- dione monohydrochloride 	BuSpar		15 - 60 mg/day		Mahmood, I., *et al.*, *Clin Pharmacokinet 36(4)*:277-87 (1999).

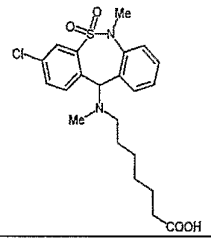
Table 3: Antidepressant Agents						
41	**Tianeptine** 	Stablon®, Ardix	serotonin reuptake accelerator, Tricyclic	25-50 mg/day		Wagstaff, A., *et al., CNS Drugs 15(3)*:231-59 (2001).
42	**Binodaline** *N,N,N'*-trimethyl-*N'*-(3-phenyl-1H-indol-1-yl)-1,2-ethanediamine		Bicyclic	50-150 mg/day		Merck Index, 12th ed, no 1266
43	**Caroxazone** 2-oxo-2H-1,3-benzoxazine-3(4H)-acetamide		a reversible monoamine oxidase inhibitor, Bicyclic			Merck Index, 12th ed, no 1907
44	**Dimethazan** 7-[2-(dimethylamino)ethyl]-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione		Bicyclic			Merck Index, 12th ed, no 3261

Table 3: Antidepressant Agents						
45	**Fencamine** 3,7-dihydro-1,3,7-trimethyl-8-[[2-[methyl(1-methyl-2-phenylethyl)amino]ethyl]amino]-1H-purine-2,6-dione		Bicyclic			Merck Index, 12th ed, no 4007
46	**Indalpine** 3-[2-(4-piperidinyl)ethyl]-1H-indole	Upstene	Bicyclic	100-150 mg/day		Merck Index, 12th ed, no 4965
47	**Indeloxazine Hydrochloride** 2-[(1H-inden-7-yloxy)methyl]morpholine hydrochloride	Elen	Bicyclic	40-120 mg/day		Merck Index, 12th ed, no 4972
48	**Nefopam** 3,4,5,6-tetrahydro-5methyl-1-phenyl-1H-2,5-benzoxazocine		Bicyclic			Merck Index, 12th ed, no 6529

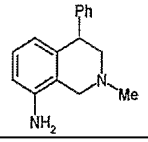
Table 3: Antidepressant Agents						
49	**Nomifensine** 1,2,3,4-tetrahydro-2-methyl-4-phenyl-8-isoquinolinamine  	Merital, Alival	Bicyclic	100-200 mg/day		Merck Index, 12th ed, no 6768
50	**Oxitriptan** 5-hydroxytryptophan	Levotonine, Pretonine, Serotonyl, Triptene	Bicyclic	150-250 mg/day		Merck Index, 12th ed, no 4895
51	**Oxypertine** 5,6-dimethoxy-2-methyl-3-[2-(4-phenyl-1-piperazinyl)ethyl]-1H-indole		Bicyclic			Merck Index, 12th ed, no 7105
52	**Thiazesim** 5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5H)-one		Bicyclic			Merck Index, 12th ed, no 9440

Table 3: Antidepressant Agents						
53	**Benmoxine** Benzoic acid 2-(1-phenylethyl)hydrazide	Neuralex, Nerusil	Hydrazides / Hydrazines	50-75 mg/day		Merck Index, 12th ed, no 1072
54	**Iproclozide** 4-(chlorophenoxy)acetic acid 2-(1-methylethyl)hydrazide	Sursum	Hydrazides / Hydrazines	10-30 mg/day		Merck Index, 12th ed, no 5092
55	**Iproniazid** 4-pyridinecarboxylic acid 2-(1-methylethyl)hydrazide	Iprozid, Marsilid	Hydrazides / Hydrazines	50-150 mg/day		Merck Index, 12th ed, no 5094
56	**L-Tryptophan** (S)-α-amino-1H-indole-3-propanoic acid					Merck Index, 12th ed, no 9929
57	**Nialamide** 4-pyridinecarboxylic acid 2-[3-oxo-3-[(phenylmethyl)amino]propyl]hydrazide	Niamid	Hydrazides / Hydrazines	100-200 mg/day		Merck Index, 12th ed, no 6575
58	**Octamoxin** (1-methylheptyl)hydrazine		Hydrazides / Hydrazines			Merck Index, 12th ed, no 6845

Table 3: Antidepressant Agents						
59	**Toloxatone** 5-(hydroxymethyl)-3-(3-methylphenyl)-2-oxazolidinone	Humory, Perenum				Merck Index, 12th ed, no 9659
60	**Cotinine** 1-methyl-5-(3-pyridinyl)2-pyrrolidinone		Pyrrolidones			Merck Index, 12th ed, no 2619
61	**Rolicyprine** 5-oxo-N-(2-phenylcyclopropyl)-2-pyrrolidinecarboxamide		Pyrrolidones			Merck Index, 12th ed, no 8409
62	**Rolipram** 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidinone		Pyrrolidones	.75-1.5 mg/day		Merck Index, 12th ed, no 8410
63	**Metralindole** 2,4,5,6-tetrahydro-9-methoxy-4-methyl-1H-3,4,6a-triazafluoranthene		Tetracyclic			Merck Index, 12th ed, no 6238

Table 3: Antidepressant Agents						
64	**Mianserin** 1,2,3,4,10,14b-hexahydro-2-methyl-dibenzo[c,f]pyrazino[1,2-a]azepine	Athymil, Bolvidon, Norval, Tolvin	Tetracyclic	30-90 mg/day		Merck Index, 12th ed, no 6260
65	**Adinazolam** 8-choro-N,N-dimethyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine-1-methanamine	Deracyn	Tricyclic	30-90 mg/day		Merck Index, 12th ed, no 159
66	**Amitriptylinoxide** 3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-N,N-dimethyl-1-propanamine N-oxide		Tricyclic			Merck Index, 12th ed, no 512
67	**Butriptyline** 10,11-dihydro-N,N,β-trimethyl-5H-dibenzo[a,d]cycloheptene-5-propanamine	Evadyne, Evadene, Centrolyse	Tricyclic			Merck Index, 12th ed, no 1568

Table 3: Antidepressant Agents						
68	**Dibenzepin** 10-[2-(dimethylamino)ethyl]-5,10-dihydro-5-methyl-11H-dibenzo[b,e][1,4]diazepin-11-one	Noveril, Ecotril, Victoril	Tricyclic	240-480 mg/day		Merck Index, 12th ed, no 3055
69	**Dimetacrine** N,N,9,9-tetramethyl-10(9H)-acridinepropanamine		Tricyclic			Merck Index, 12th ed, no 3258
70	**Dothiepin** 3-dibenzo[b,e]thiepin-11(6H)-ylidene-N,N-dimethyl-1-propanamine	Prothiaden, Arpin, Idom	Tricyclic	50-225 mg/day		Merck Index, 12th ed, no 3485
71	**Fluacizine** 10-[3-diethylamino)-1-oxopropyl]-2-(trifluoromethyl)-10H-phenothiazine		Tricyclic			Merck Index, 12th ed, no 4149

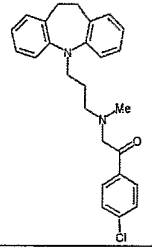
Table 3: Antidepressant Agents						
72	**Imipramine N-Oxide** 10,11-dihydro-N,N-dimethyl-5H-dibenz[b,f]azepine-5-propanamine N-oxide		Tricyclic			Merck Index, 12th ed, no 4956
73	**Iprindole** 6,7,8,9,10,11-hexahydro-N,N-dimethyl-5H-cyclooct[b]indole-5-propanamine		Tricyclic			Merck Index, 12th ed, no 5091
74	**Lofepramine** 1-(4-chlorophenyl)-2-[[3-(10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)propyl]methylamino]ethanone 	Emdalen, Gamanil, Lomont, Tymelyt	Tricyclic	70-210 mg/day		Merck Index, 12th ed, no 5587

Table 3: Antidepressant Agents						
75	**Melitracen** 3-(10,10-dimethyl-9(10H)-anthracenylidene)-N,N-dimethyl-1-propanamine	Dixoran, Melixeran, Trausabun	Tricyclic	75-225 mg/day		Merck Index, 12th ed, no 5866
76	**Metapramine** 10,11-dihyrdo-N,5-dimethyl-5H-dibenz[b,f]azepin-10-amine	Timaxil	Tricyclic	150-450 mg/day		Merck Index, 12th ed, no 5991
77	**Noxiptilin** 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one O-[2-(dimethylamino)ethyl]oxime	Nogedal	Tricyclic	25-200 mg/day		Merck Index, 12th ed, no 6821
78	**Opipramol** 4-[3-(5H-dibenz[b,f]azepin-5yl)propyl]-1-piperazineethanol	Insidon, Oprimol	Tricyclic	150-300 mg/day		Merck Index, 12th ed, no 6985

Table 3: Antidepressant Agents						
79	**Pizotyline** 4-(9,10-dihydro-4H-benzo[4,5]cyclohepta[1,2-b]thien-4-ylidene)-1-methylpiperidine		Tricyclic			Merck Index, 12th ed, no 7671
80	**Propizepine** 6-[2-(dimethylamino)propyl]-1,6-dihydro-5H-pyrido[2,3-b][1,5]benzodiazepin-5-one	Vagran	Tricyclic	50-200 mg/day		Merck Index, 12th ed, no 8019
81	**Quinupramine** 5-(1-azabicyclo[2.2.2]oct-3-yl)-10,11-dihydro-5H-dibenz[b,f]azepine	Adeprim, Kevopril	Tricyclic			Merck Index, 12th ed, no 8267
82	**Tofenacin** N-methyl-2-[(2-methylphenyl)phenylmethoxy]ethanamine					Merck Index, 12th ed, no 9641

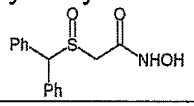
Table 3: Antidepressant Agents						
83	**Adrafinil** 2-[(diphenylmethyl)sulfinyl]-N-hydroxyacetamide 	Olmifon		600-1200 mg/day		Merck Index, 12th ed, no 168
84	**Benactyzine** 1-[7-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]-2-benzofuranyl]ethanone					Merck Index, 12th ed, no 1050
85	**Butacetin** N-[4-(1,1-dimethylethoxy)phenyl]acetamide					Merck Index, 12th ed, no 1532
86	**Dioxadrol** 2-(2,2-diphenyl-1,3-dioxolan-4-yl)piperidine					Merck Index, 12th ed, no 3352
87	**Duloxetine** (S)-N-methyl-γ-(1-naophthalenyloxy)-2-thiophenepropanamine	Cymbalta		40-120 mg/day		Merck Index, 12th ed, no 3518

Table 3: Antidepressant Agents						
88	**Etoperidone** 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-4,5-diethyl-2,4-dihydro-3H-1,2,4-triazol-3-one					Merck Index, 12th ed, no 3930
89	**Febarbamate** 1-[2-[(aminocarbonyl)oxy]-3-butoxypropyl]-5-ethyl-5-phenyl-2,4,6(1H,3H,5H)-pyrimidinetrione					Merck Index, 12th ed, no 3983
90	**Femoxetine** (3R-trans)-3-[(4-methoxyphenoxy)methyl]-1-methyl-4-phenylpiperidine			400-600 mg/day		Merck Index, 12th ed, no 3993
91	**Fenpentadiol** 2-(4-chlorophenyl)-4-methyl-2,4-pentanediol					Merck Index, 12th ed, no 4029

Table 3: Antidepressant Agents						
92	**Hematoporphyrin** 7,12-bis(1-hydroxyethyl)-3,8,13,17-tetramethyl-21H,23H-porphine-2,18-dipropanoic acid					Merck Index, 12th ed, no 4669
93	**Hypericin** 1,3,4,6,8,13-hexahydroxy-10,11-dimethylphenanthro[1,10,9,8-opqra]perylene-7,14-dione					Merck Index, 12th ed, no 4911
94	**Levophacetoperane** α--phenyl-2-piperidinemethanol acetate					Merck Index, 12th ed, no 5493
95	**Medifoxamine** N,N-dimethyl-2,2-diphenoxyethanamine	Cledial, Gerdasyl		100-150 mg/day		Merck Index, 12th ed, no 5834
96	**Minaprine** N-(4-methyl-6-phenyl-3-pyridazinyl)-4-morpholineethanamine	Cantor		100-250 mg/day		Merck Index, 12th ed, no 6287

Table 3: Antidepressant Agents						
97	**Oxaflozane** 4-(1-methylethyl)-2-[3-(trifluoromethyl)phenyl]morpholine	Conflictan		15-30 mg/day		Merck Index, 12th ed, no 7039
98	**Piberaline** 1-(phenylmethyl)-4-(2-pyridinylcarbonyl)piperazine					Merck Index, 12th ed, no 7547
99	**Prolintane** 1-[1-(phenylmethyl)butyl]pyrrolidine					Merck Index, 12th ed, no 7964
100	**Pyrisuccideanol** Butanedioic acid 2-(dimethylamino)ethyl [5-hydroxy-4-(hydroxymethyl)-6-methyl-3-pyridinyl]methyl ester					Merck Index, 12th ed, no 8175

Table 3: Antidepressant Agents						
101	**Ritanserin** 6-[2-[4-[bis(4-fluorophenyl)methylene]-1-piperidinyl]ethyl]-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one	Tisterton		5-30 mg/day		Merck Index, 12th ed, no 8399
102	**Roxindole** 3-[4-(3,6-dihydro-4-phenyl-1(2H)-pyridinyl)butyl]-1H-indol-5-ol			7.5-30 mg/day		Merck Index, 12th ed, no 8432
103	**Rubdium Chloride** Rubinorm					Merck Index, 12th ed, no 8441
104	**Sulpiride** 5-(aminosulfonyl)-N-[(1-ethyl-2-pyrrolidinyl)methyl]-2-methoxybenzamide	Sulparex, Dogmatil, Dolmatil, Valirem		50-200 mg/day		Merck Index, 12th ed, no 9163
105	**Thozalinone** 2-(dimethylamino)-5-phenyl-4(5H)-oxazolone					Merck Index, 12th ed, no 9521

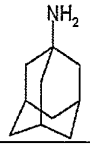
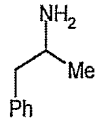
Table 3: Antidepressant Agents						
106	**Amantadine** 	Symmetrel, Symandine, Amantan, Mantadan, Virofral		100-300 mg/day		
107	**Amiflamine**		reversible MAO-A inhibitor			
108	**Amisulpride**	Solian		50-200 mg/day		
109	**Amphetamine** 	Dexedrine, DextroStat, Benzadrine		5-40 mg/day		
110	**Aprepitant**	Emend				
111	**Aripiprazole**	Abilify, Abilitat		15-30 mg/day		
112	**Atomoxetine**	Strattera		50-150 mg/day		
113	**Befloxatone**			10-40 mg/day		
114	**Brofaromine**	Consonar		50-150 mg/day		
115	**Bromocriptine**	Parlodel, Ergoset		2.5-40 mg/day		

Table 3: Antidepressant Agents						
116	**Buprenorphine**	Temgesic, Buprenex, Subutex		1.2-3.2 mg/day		
117	**Cericlamine**					
118	**Ciclazindol**			100-150 mg/day		
119	**Cimoxatone**					
120	**Clorgyline**			5-30 mg/day		
121	**Clovoxamine**			100-300 mg/day		
122	**Dapoxetine**					
123	**Demexiptiline**	Tinoran, Deparon				
124	**Dexmethylphenidate**	Focalin		5-20 mg/day		
125	**Etryptamine**	Monase				
126	**Fengabine**			900-1800 mg/day		
127	**Flerobuterol**					
128	**Flesinoxan**					

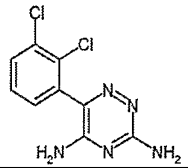
Table 3: Antidepressant Agents						
129	**Flibanserin**	Ectris		50-200 mg/day		
130	**Fluparoxan**					
131	**Gepirone**	Ariza		10-90 mg/day		
132	**Idazoxan**			40-120 mg/day		
133	**Igmesine**					
134	**Incazane**					
135	**Ipsapirone**					
136	**Isradipine**	Dynacirc, Lomir, Icaz		5-20 mg/day		
137	**Levodopa**	Larodopa, Dopar		2-8 grams		
138	**Lamotrigine** 	Lamictal		50-500 mg/day		
139	**Levoprotiline**					

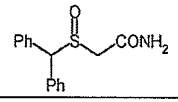
Table 3: Antidepressant Agents						
140	**Liothyronine**	Cytomel		25-100 mcg/day		
141	**Litoxetine**			10-25 mg/day		
142	**Mazindol**	Mazanor, Sanorex, Teronac		1-3 mg/day		
143	**Mebanazine**	Actomol				
144	**Mefexamide**	Timodyne, Perneuron				
145	**Memantine**	Axura, Akatinol, Exiba, Neuroplus				
146	**Mifepristone**	Mifeprex				
147	**Modafinil** 	Provigil, Alertec, Modiodal				
148	**Nemifitide**					
149	**Nisoxetine**					
150	**Nitroxazepine**	Sintamil		75-225 mg/day		

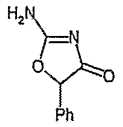
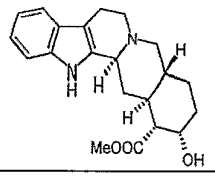
Table 3: Antidepressant Agents						
151	**Olanzapine**	Zyprexa, Lanzac		5-20 mg/day		
152	**Oxaprotiline**					
153	**Oxycodone**	Oxycontin, Ducodal, Eubine,		40-180 mg/day		
154	**Ziprasidone**	Geodon, Zeldox		40-200 mg/day		
155	**Pemoline** 	Cylert, Deltamine		50-113 mg/day		
156	**Pergolide**	Permax, Celance		.25-5 mg/day		
157	**Phenoxypropazine**	Drazine				
158	**Phentermine**	Adipex, Zantryl				
159	**Pindolol**	Visken				
160	**Piribedil**	Trivastal				

Table 3: Antidepressant Agents						
161	**Pirlindole, or Pyrazidol**					
162	**Pramipexole**	Mirapex, Sifrol		1.5-4.5 mg/day		
163	**Pregabalin**					
164	**Pyrovalerone**	Centroton, Thymergix				
165	**Risperidone**	Risperdal		.5-2 mg/day		
166	**Ropinirole**	Requip		.75-3 mg/day		
167	**Sibutramine**	Meridia, Reductil		5-15 mg/day		
168	**Talipexole**					
169	**Tetrindole**					
170	**Thyroxine**	Synthroid, Levoxyl, Levothroid				
171	**Tolcapone**	Tasmar				
172	**Vilazodone**					
173	**Viqualine**					

Table 3: Antidepressant Agents						
174	**Yohimbine** 	Aphrodyne, Procomil, Yocon		8.1-16.2 mg/day		
175	**Asenapine**					
176	**1-pyrimidinylpiperazine**					
177	**6-hydroxy-buspirone**					

[0206] In a preferred embodiment, the class of antidepressant that is suitable for use with the methods and compositions of the present invention is selected from the group consisting of tricyclics, tetracylics, hydrazides/hydrazines, bicyclics, benzodiazepines, and pyrrolidones, and mixtures thereof.

[0207] In a preferred embodiment, the tricyclic antidepressant that is suitable for use with the methods and compositions of the present invention is selected from the group consisting of amitriptyline, desipramine, imipramine, nortriptyline, amineptine, clomipramine, doxepin, amoxapine, trimipramine, protriptyline, tianeptine, adinazolam, amitriptylinoxide, butriptyline, dibenzepin, dimetacrine, dothiepin, fluacizine, imipramine N-oxide, iprindole, lofepramine, melitracen, metapramine, noxiptilin, opipramol, pizotyline, propizepine, and quinupramine, and mixtures thereof.

[0208] In a preferred embodiment, the tetracyclic antidepressant that is suitable for use with the methods and compositions of the present invention is selected from the group consisting of maprotiline, mirtazapine, metralindole, and mianserin, and mixtures thereof.

[0209] In a preferred embodiment, the bicyclic antidepressant that is suitable for use with the methods and compositions of the present invention is selected from the group consisting of sertraline, citalopram, paroxetine, trazodone, binodaline, caroxazone, dimethazan, fencamine, indalpine, indeloxazine hydrochloride, nefopam, nomifensine, oxitriptan, oxypertine, and thiazesim, and mixtures thereof.

[0210] In a preferred embodiment, the benzodiazepine antidepressant that is suitable for use with the methods and compositions of the present invention is selected from the group consisting ofalprazolam and diazepam, and mixtures thereof.

[0211] In a preferred embodiment, the class of antidepressant that is suitable for use with the methods and compositions of the present invention is selected from the group consisting of selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, noradrenaline reuptake

inhibitors, selective serotonin and noradrenaline reuptake inhibitors, dual-action serotonin norepinephrine reuptake inhibitors, norepinephrine antagonist serotonin antagonists, selective serotonin and noradrenaline reuptake inhibitors, serotonin antagonist and reuptake inhibitors, norepinephrine dopamine reuptake inhibitor, and serotonin reuptake accelerators, and mixtures thereof.

[0212] In a preferred embodiment, the selective serotonin reuptake inhibitor antidepressant that is suitable for use with the methods and compositions of the present invention is selected from the group consisting of sertraline, citalopram, escitalopram oxalate, fluvoxamine, paroxetine, and fluoxetine, and mixtures thereof.

[0213] In a preferred embodiment, the selective serotonin reuptake inhibitor antidepressant that is suitable for use with the methods and compositions of the present invention is selected from the group consisting of phenelzine, tranylcypromine, isocarboxazid, selegiline, caroxazone, and amiflamine, and mixtures thereof.

[0214] In a preferred embodiment, the serotonin antagonist and reuptake inhibitor antidepressant that is suitable for use with the methods and compositions of the present invention is selected from the group consisting of nefazodone and trazodone, and mixtures thereof.

[0215] In a preferred embodiment, the serotonin and noradrenaline reuptake inhibitor antidepressant that is suitable for use with the methods and compositions of the present invention is selected from the group consisting of milnacipran and moclobemide, and mixtures thereof.

[0216] In a preferred embodiment, the antidepressant that is suitable for use with the methods and compositions of the present invention is selected from the group consisting of sertraline, citalopram, escitalopram oxalate, fluvoxamine, paroxetine, fluoxetine, amitriptyline, desipramine, imipramine, maprotiline, reboxetine, nortriptyline, amineptine, zimelidine, venlafaxine, mirtazapine, milnacipran, phenelzine, tranylcypromine, nefazodone, trazodone, bupropion, clomipramine, tandospirone, isocarboxazid, lithium carbonate, lithium citrate, doxepin,

amoxapine, moclobemide, trimipramine, selegiline, protriptyline, viloxazine, alprazolam, pargyline, dextroamphetamine, methylphenidate, diazepam, buspirone, tianeptine, binodaline, caroxazone, dimethazan, fencamine, indalpine, indeloxazine hydrochloride, nefopam, nomifensine, oxitriptan, oxypertine, thiazesim, benmoxine, iproclozide, iproniazid, L-tryptophan, nialamide, octamoxin, toloxatone, cotinine, rolicyprine, rolipram, metralindole, mianserin, adinazolam, amitriptylinoxide, butriptyline, dibenzepin, dimetacrine, dothiepin, fluacizine, imipramine N-oxide, iprindole, lofepramine, melitracen, metapramine, noxiptilin, opipramol, pizotyline, propizepine, quinupramine, tofenacin, adrafinil, benactyzine, butacetin, dioxadrol, duloxetine, etoperidone, febarbamate, femoxetine, fenpentadiol, hematoporphyrin, hypericin, levophacetoperane, medifoxamine, minaprine, oxaflozane, piberaline, prolintane, pyrisuccideanol, ritanserin, roxindole, rubdium chloride, sulpiride, thozalinone, amantadine, amiflamine, amisulpride, amphetamine, aprepitant, aripiprazole, atomoxetine, befloxatone, brofaromine, bromocriptine, buprenorphine, cericlamine, ciclazindol, cimoxatone, clorgyline, clovoxamine, dapoxetine, demexiptiline, dexmethylphenidate, etryptamine, fengabine, flerobuterol, flesinoxan, flibanserin, fluparoxan, gepirone, idazoxan, igmesine, incazane, ipsapirone, isradipine, levodopa, lamotrigine, levoprotiline, liothyronine, litoxetine, mazindol, mebanazine, mefexamide, memantine, mifepristone, modafinil, nemifitide, nisoxetine, nitroxazepine, olanzapine, oxaprotiline, oxycodone, ziprasidone, pemoline, pergolide, phenoxypropazine, phentermine, pindolol, piribedil, pirlindole or pyrazidol, pramipexole, pregabalin, pyrovalerone, risperidone, ropinirole, sibutramine, talipexole, tetrindole, thyroxine, tolcapone, vilazodone, viqualine, asenapine, 1-pyrimidinylpiperazine, 6-hydroxy-buspirone, and yohimbine, prodrugs of any of them, and mixtures thereof.

[0217] Any combination that includes at least one of the Cox-2 inhibitors that are described alone and, optionally, at least one of the antidepressant agents that are described above can be used in the novel methods, compositions, pharmaceutical compositions and kits of the

present invention. For example, a Cox-2 inhibitor such as celecoxib can be combined with any of the aforementioned antidepressant agents described in Table 3, including, for example, the antidepressant agent, sertraline.

[0218] One of skill in the art will understand how to make the antidepressant agents described above by following the teachings of the corresponding references.

[0219] Cox-2 inhibitors and antidepressant agents that are useful in the present invention can be of any purity or grade, as long as the preparation is of a quality suitable for pharmaceutical use. The Cox-2 inhibitor or antidepressant agent can be provided in pure form, or it can be accompanied with impurities or commonly associated compounds that do not affect its physiological activity or safety.

[0220] The Cox-2 inhibitors and antidepressant agents can be supplied in the form of a pharmaceutically active salt, a prodrug, an isomer, a tautomer, a racemic mixture, or in any other chemical form or combination that, under physiological conditions, still provides for inhibition of the Cox-2 enzyme and any physiological function that the antidepressant agent may perform. The present invention includes all possible diastereomers as well as their racemic and resolved, enantiomerically pure forms.

[0221] The present invention also encompasses a novel therapuetic composition comprising at least one Cox-2 inhibitor and one or more antidepressant agents.

[0222] In the present invention, a composition comprising a Cox-2 inhibitor in combination with a antidepressant agent is administered to a subject in need of such treatment according to standard routes of drug delivery that are well known to one of ordinary skill in the art.

[0223] The present invention also encompasses a pharmaceutical composition for preventing or treating a psychiatric disorder in a subject that is in need of such prevention and treatment, the pharmaceutical

composition comprising at least one Cox-2 inhibitor, at least one antidepressant agent, and a pharmaceutically acceptable carrier. Thus, the combination of a Cox-2 inhibitor and an antidepressant agent can be provided in a pharmaceutically acceptable carrier or excipient to form a pharmaceutical composition.

[0224] The pharmaceutical compositions of the present invention comprise a Cox-2 inhibitor and an antidepressant agent as an active ingredient or a pharmaceutically acceptable salt, thereof, and also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. When the Cox-2 inhibitor and an antidepressant agent inhibitor are supplied along with a pharmaceutically acceptable carrier, a pharmaceutical composition is formed. A pharmaceutical composition of the present invention is directed to a composition suitable for the prevention, treatment, or amelioration of a psychiatric disorder. The pharmaceutical composition comprises a pharmaceutically acceptable carrier, a Cox-2 inhibitor, and an antidepressant agent.

[0225] The term "pharmaceutically acceptable" is used herein to mean that the modified noun is appropriate for use in a pharmaceutical product.

[0226] Pharmaceutically acceptable carriers and excipients include, but are not limited to, physiological saline, Ringer's solution, phosphate solution or buffer, buffered saline and other carriers known in the art. Pharmaceutical compositions may also include stabilizers, anti-oxidants, colorants, and diluents. Pharmaceutically acceptable carriers and additives are chosen such that side effects from the pharmaceutical compound are minimized and the performance of the compound is not canceled or inhibited to such an extent that treatment is ineffective. In one embodiment the Cox-2 inhibitor alone or in combination with the antidepressant agent are administered to a subject together in one pharmaceutical carrier. In another embodiment, the Cox-2 inhibitor and the antidepressant agent are administered separately.

[0227] The pharmaceutically acceptable carrier can also be selected on the basis of the desired route of administration of the compound. For example, in a preferred embodiment the carrier is suitable for oral administration. In a more preferred embodiment, the composition includes a carrier or additional agent that is suitable for promoting delivery of the compound to the brain. Carriers that can promote delivery of the compound to the brain can include any carrier that promotes translocation across the blood-brain barrier and any carrier that promotes uptake of the compound by neural cells. Examples of such carriers include those disclosed in U.S. Pat. Nos. 5,604,198 (issued to Poduslo, *et al.*), 5,827,819 (issued to Yatvin, *et al.*), 5,919,815 (issued to Bradley, *et al.*), 5,955,459 (issued to Bradley, *et al.*), and 5,977,174 (issued to Bradley, *et al.*).

[0228] The terms "pharmaceutically acceptable salts" refer to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Illustrative pharmaceutically acceptable salts are prepared from formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, hydrochloric, trifluoroacetic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, β-hydroxybutyric, galactaric and galacturonic acids.

[0229] Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine,

caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

[0230] Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to, appropriate alkali metal salts, alkaline earth metal salts and other physiological acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences.

[0231] Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N, N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include, without limitation, hydrochloric acid, hydroiodic acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

[0232] All of the above salts and ions can be prepared by those skilled in the art by conventional means from the corresponding compound of the present invention.

[0233] In the present invention, a Cox-2 inhibitor and/or antidepressant agent are administered to a patient in need of such treatment or prevention according to standard routes of drug delivery that are well known to one of ordinary skill in the art. The particular route and dosage of the Cox-2 inhibitor and the antidepressant agent depend upon

the needs of the subject being treated, the type of treatment or prevention, the efficacy of the compound and the degree of disease severity in the subject.

[0234] The pharmaceutical compositions may be administered enterally and parenterally. Oral (intra-gastric) is a preferred route of administration. Pharmaceutically acceptable carriers can be in solid dosage forms for the methods of the present invention, which include tablets, capsules, pills, and granules, which can be prepared with coatings and shells, such as enteric coatings and others well known in the art. Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs.

[0235] Enteral administration includes solution, tablets, sustained release capsules, enteric-coated capsules, and syrups. When administered, the pharmaceutical composition may be at or near body temperature.

[0236] Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients, which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate, granulating and disintegrating agents, for example, maize starch, or alginic acid, binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid, or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time

delay material such as glyceryl monostearate or glyceryl distearate may be employed.

[0237] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredients are mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients are present as such, or mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

[0238] Aqueous suspensions can be produced that contain the active materials in a mixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone gum tragacanth and gum acacia; dispersing or wetting agents may be naturally-occurring phosphatides, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, or one or more sweetening agents, such as sucrose or saccharin.

[0239] Oily suspensions may be formulated by suspending the active ingredients in an omega-3 fatty acid, a vegetable oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol.

[0240] Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

[0241] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[0100] Syrups and elixirs containing the Cox-2 inhibitor and/or antidepressant agent may be formulated with sweetening agents, for example glycerol, sorbitol, or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

[0242] The subject method of prescribing a Cox-2 inhibitor and/or antidepressant agent and compositions comprising the same can also be administered parenterally, either subcutaneously, or intravenously, or intramuscularly, or intrasternally, or by infusion techniques, in the form of sterile injectable aqueous or olagenous suspensions. Parenteral administration includes subcutaneous, intramuscular, intradermal, intramammary, intravenous, and other administrative methods known in the art.

[0243] Administration of either one or both of the Cox-2 inhibitor and antidepressant agents can also be by inhalation, in the form of aerosols or solutions for nebulizers. Therefore, in one embodiment, the Cox-2 inhibitor and/or the antidepressant agent is administered by direct inhalation into the respiratory system of a subject for delivery as a mist or other aerosol or dry powder. Delivery of drugs or other active ingredients directly to the subject's lungs provides numerous advantages including, providing an extensive surface area for drug absorption, direct delivery of therapeutic agents to the disease site in the case of regional drug therapy,

eliminating the possibility of drug degradation in the subject's intestinal tract (a risk associated with oral administration), and eliminating the need for repeated subcutaneous injections.

[0244] Aerosols of liquid particles comprising the active materials may be produced by any suitable means, such as inhalatory delivery systems. Nebulizers are commercially available devices which transform solutions or suspensions of the active ingredient into a therapeutic aerosol mist either by means of acceleration of compressed gas, typically air or oxygen, through a narrow venturi orifice or by means of ultrasonic agitation. Suitable formulations for use in nebulizers consist of the active ingredient in a liquid carrier. The carrier is typically water, and most preferably sterile, pyrogen-free water, or a dilute aqueous alcoholic solution, preferably made isotonic, but may be hypertonic with body fluids by the addition of, for example, sodium chloride. Optional additives include preservatives if the formulation is not made sterile, for example, methyl hydroxybenzoate, as well as antioxidants, flavoring agents, volatile oils, buffering agents and surfactants, which are normally used in the preparation of pharmaceutical compositions.

[0245] Aerosols of solid particles comprising the active materials may likewise be produced with any solid particulate medicament aerosol generator. Aerosol generators for administering solid particulate medicaments to a subject produce particles which are respirable, as explained above, and generate a volume of aerosol containing a predetermined metered dose of a medicament at a rate suitable for human administration.

[0246] One type of solid particulate aerosol generator is an insufflator. Suitable formulations for administration by insufflation include finely comminuted powders which may be delivered by means of an insufflator or taken into the nasal cavity in the manner of a snuff. In the insufflator, the powder is contained in capsules or cartridges, typically made of gelatin or plastic, which are either pierced or opened *in situ* and the powder delivered by means of air drawn through the device upon

inhalation or by means of a manually-operated pump. The powder employed in the insufflator consists either solely of the active ingredient or of a powder blend comprising the active materials, a suitable powder diluent, such as lactose, and an optional surfactant.

[0247] A second type of aerosol generator is a metered dose inhaler. Metered dose inhalers are pressurized aerosol dispensers, typically containing a suspension or solution formulation of the Cox-2 inhibitor and/or the antidepressant agent in a liquified propellant. During use, the metered dose inhaler discharges the formulation through a valve, adapted to deliver a metered volume, to produce a fine particle spray containing the active materials. Any propellant may be used for aerosol delivery, including both chlorofluorocarbon-containing propellants and non-chlorofluorocarbon-containing propellants.

[0248] A third type of aerosol generator is a electrohydrodynamic (EHD) aerosol generating device, which has the advantage of being adjustable to create substantially monomodal aerosols having particles more uniform in size than aerosols generated by other devices or methods. Typical EHD devices include a spray nozzle in fluid communication with a source of liquid to be aerosolized, at least one discharge electrode, a first voltage source for maintaining the spray nozzle at a negative (or positive) potential relative to the potential of the discharge electrode, and a second voltage source for maintaining the discharge electrode at a positive (or negative) potential relative to the potential of the spray nozzle. Most EHD devices create aerosols by causing a liquid to form droplets that enter a region of high electric field strength. The electric field then imparts a net electric charge to these droplets, and this net electric charge tends to remain on the surface of the droplet. The repelling force of the charge on the surface of the droplet balances against the surface tension of the liquid in the droplet, thereby causing the droplet to form a cone-like structure known as a Taylor Cone. In the tip of this cone-like structure, the electric force exerted on the surface of the droplet overcomes the surface tension of the liquid, thereby generating a stream

of liquid that disperses into a many smaller droplets of roughly the same size. These smaller droplets form a mist which constitutes the aerosol cloud that the user ultimately inhales.

[0249] Administration of the compositions of the present invention can also be rectally, in the form of suppositories prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperature, but liquid at the rectal temperature and will therefore, melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

[0250] Also encompassed by the present invention is buccal or "sub-lingual" administration, which includes lozenges or a chewable gum comprising the compounds, set forth herein. The compounds can be deposited in a flavored base, usually sucrose, and acacia or tragacanth, and pastilles comprising the compounds in an inert base such as gelatin and glycerin or sucrose and acacia.

[0251] The prevent invention further encompasses intranasal administration comprising the compounds set forth herein. Intranasal dosage forms include, but are not limited to, aerosols, drops, gels, powders, and mixtures thereof.

[0252] Other methods for administration of the Cox-2 inhibitor compound and/or the antidepressant agent include dermal patches that release the medicaments directly into a subject's skin.

[0253] Topical delivery systems are also encompassed by the present invention and include ointments, powders, sprays, creams, jellies, collyriums, solutions or suspensions.

[0254] The compositions of the present invention can optionally be supplemented with additional agents such as, for example, viscosity enhancers, preservatives, surfactants and penetration enhancers.

[0255] Viscosity is an important attribute of many medications. Drops that have a high viscosity tend to stay in the body for longer periods and thus, increase absorption of the active compounds by the target tissues or increase the retention time. Such viscosity-building agents

include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methylcellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose or other agents know to those skilled in the art. Such agents are typically employed at a level of from 0.01% to 2% by weight.

Preservatives are optionally employed to prevent microbial contamination during use. Suitable preservatives include polyquaternium-1, benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, or other agents known to those skilled in the art. The use of polyquaternium-1 as the antimicrobial preservative is preferred. Typically, such preservatives are employed at a level of from 0.001% to 1.0% by weight.

[0256] The solubility of the components of the present compositions may be enhanced by a surfactant or other appropriate co-solvent in the composition. Such co-solvents include polysorbate 20, 60, and 80, polyoxyethylene/polyoxypropylene surfactants (e.g. Pluronic F-68, F-84 and P-103), cyclodextrin, or other agents known to those skilled in the art. Typically, such co-solvents are employed at a level of from 0.01% to 2% by weight.

[0257] A penetration enhancer is an agent used to increase the permeability of the skin to an active agent to increase the rate at which the drug diffuses through the skin and enters the tissues and bloodstream. Thus, in one embodiment of the present invention, a penetration enhancer may be added to a Cox-2 inhibitor topical composition or a Cox-2 inhibitor and antidepressant agent or topical composition.

[0258] Examples of penetration enhancers suitable for use with the compositions of the present invention include: alcohols, such as ethanol and isopropanol; polyols, such as n-alkanols, limonene, terpenes, dioxolane, propylene glycol, ethylene glycol, other glycols, and glycerol; sulfoxides, such as dimethylsulfoxide (DMSO), dimethylformamide, methyl dodecyl sulfoxide, dimethylacetamide; esters, such as isopropyl myristate/palmitate, ethyl acetate, butyl acetate, methyl proprionate, and

capric/caprylic triglycerides; ketones; amides, such as acetamides; oleates, such as triolein; various surfactants, such as sodium lauryl sulfate; various alkanoic acids, such as caprylic acid; lactam compounds, such as azone; alkanols, such as oleyl alcohol; dialkylamino acetates, and admixtures thereof.

[0259] Pharmaceutically acceptable excipients and carriers encompass all the foregoing and the like. The above considerations concerning effective formulations and administration procedures are well known in the art and are described in standard textbooks. See e.g. Gennaro, A. R., Remington: The Science and Practice of Pharmacy, 20th Edition, (Lippincott, Williams and Wilkins), 2000; Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania, 1975; Liberman, et al., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Kibbe, et al., Eds., Handbook of Pharmaceutical Excipients (3rd Ed.), American Pharmaceutical Association, Washington, 1999.

[0260] For purposes of the present invention, it is preferred that the amount of a Cox-2 inhibitor and the amount of an antidepressant agent comprise an effective amount of each of the two treatment agents. In another embodiment of the present invention, the amount of the combination therapy with the Cox-2 inhibitor and antidepressant agent together comprises a therapeutically effective amount of the combined therapy.

[0261] As used herein, an "effective amount" means the dose or amount to be administered to a subject and the frequency of administration to the subject, which is readily determined by one having ordinary skill in the art, by the use of known techniques and by observing results obtained under analogous circumstances.

[0262] In determining the effective amount or dose, a number of factors are considered by the attending diagnostician, including, but not limited to, the potency and duration of action of the compounds used, the nature and severity of the illness to be treated, as well as the sex, age,

weight, general health and individual responsiveness of the patient to be treated, and other relevant circumstances.

[0263] As used herein, the terms "therapeutically effective" are intended to qualify the amount of an agent for use in therapy that will achieve the goal of preventing or improving the severity of the disorder being treated, while avoiding adverse side effects typically associated with alternative therapies. A psychiatric disorder symptom is considered ameliorated or improved if any benefit is achieved, no matter how slight.

[0264] As used herein, the terms "prophylactically effective" refer to an amount of a Cox-2 inhibitor alone or in combination with at least one antidepressant agents that causes a decrease in the frequency of incidence of psychiatric disorders or psychiatric disorder-related symptoms. The term "prophylactic" refers to the prevention of psychiatric disorders or a psychiatric disorder-related symptom, whereas the term "therapeutic" refers to the effective treatment of an existing disorder such as psychiatric disorders or a psychiatric disorder-related symptom.

[0265] It will be appreciated that the amount of the Cox-2 inhibitor alone or in combination with at least one antidepressant agent required for use in the treatment or prevention of psychiatric disorders and psychiatric disorder-related symptoms will vary within wide limits and will be adjusted to the individual requirements in each particular case. In general, for administration to adults, an appropriate daily dosage is described herein, although the limits that are identified as being preferred may be exceeded if expedient. The daily dosage can be administered as a single dosage or in divided dosages.

[0266] The appropriate dosage level of a Cox-2 inhibitor will generally be from about 0.01 mg per kg to about 140 mg per kg subject body weight per day, which may be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 mg/kg to about 25 mg/kg per day; more preferably about 0.5 mg/kg to about 10 mg/kg per day.

[0267] In larger mammals, for example humans, a typical indicated dose is about 0.5 mg to 7 grams orally per day. A Cox-2 inhibitor compound may be administered on a regimen of several times per day, for example 1 to 4 times per day, preferably once or twice per day.

[0268] The amount of the Cox-2 inhibitor that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 7 g of active agent compounded optionally with an appropriate and convenient amount of carrier material, which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms for the Cox-2 inhibitor will generally contain between from about 1 mg to about 500 mg of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

[0269] The dosage level of an antidepressant agent will necessarily depend on the particular antidepressant agent that is used. The appropriate dosage level of an antidepressant agent will generally be from about 0.001 mg per kg to about 50 mg per kg subject body weight per day, which may be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 mg/kg to about 25 mg/kg per day; more preferably about 1.0 mg/kg to about 10 mg/kg per day.

[0270] In larger mammals, for example humans, a typical indicated dose of an antidepressant agent is about 0.1 mg to 2 grams orally per day. An antidepressant agent may be administered on a regimen of several times per day, for example 1 to 4 times per day, preferably once or twice per day.

[0271] The exact dosage and regimen for administering a Cox-2 inhibitor alone or in combination with at least one antidepressant agent will necessarily depend upon the potency and duration of action of the compounds used, the nature and severity of the illness to be treated, as well as the sex, age, weight, general health, and individual responsiveness of the patient to be treated, and other relevant circumstances. Those

skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), Appendix II, pp. 1707-1711.

[0272] The effectiveness of a particular dosage of a Cox-2 inhibitor alone or in combination with an antidepressant agent is determined by monitoring the effect of a given dosage on the progress or prevention of a particular psychiatric disorder. This monitoring may be done through out-patient therapy or in a hospitalized setting.

[0273] For example, monitoring the effectiveness of the methods and compositions of the present invention on a subject suffering from depression may involve evaluating the subject under out-patient therapy. In this setting, any changes in the subject's symptoms of depression are monitored and evaluated by a therapist.

[0274] Still other methods for monitoring the effectiveness of the methods and compositions of the present invention can include conducting an evaluation of a subject's limbic-diencephalic function/dysfunction. Such evaluation can be performed by utilizing such tests as the thyrotropin-releasing hormone (TRH) stimulation test, the dexamethasone suppression test (DST), and sleep EEG for rapid eye movement (REM) latency test. See The Merck Manual of Diagnosis & Therapy, Beers & Brakow, 17th edition, Published by Merck Research Labs, Sec. 15, Chap. 189, Psychiatric Disorders, Mood Disorders (1999).

[0275] As used herein, the term "subject" for purposes of treatment includes any subject, and preferably is a subject who is in need of the treatment of psychiatric disorders, or who needs treatment of a psychiatric disorder-related symptom. For purposes of prevention, the subject is any subject, and preferably is a subject that is at risk for, or is predisposed to, developing a psychiatric disorder or a psychiatric disorder-related symptom. The subject is typically an animal, and yet more typically is a mammal. "Mammal", as that term is used herein, refers to any animal classified as a mammal, including humans, domestic and farm animals, zoo, sports, or pet animals, such as dogs, horses, cats, cattle, etc.

Preferably, the mammal is a human. For purposes of the present invention, an adult human weighs approximately seventy kilograms.

[0276] As used herein, the terms "a subject who is predisposed to a psychiatric disorder" and "a subject who is at risk for a psychiatric disorder," both of which are used interchangeably herein, mean any subject at risk for developing psychiatric disorders or any psychiatric disorder-related symptoms. The subject may be a human subject who is at risk for developing psychiatric disorders or any psychiatric disorder-related symptoms. The subject may be at risk due to genetic predisposition, diet, age, exposure to traumatic life events, exposure to a separation such as death, and the like. The subject may also be at risk due to physiological factors such as abnormalities in the brain.

[0277] As used herein, the terms "subject is in need of the prevention or treatment of a psychiatric disorder or a psychiatric disorder-related symptom" refer to any subject who is suffering from or is predisposed to psychiatric disorders or any psychiatric disorder-related symptoms described herein. The terms "subject is in need of the prevention or treatment of a psychiatric disorder or a psychiatric disorder-related symptom" also refer to any subject that requires a lower dose of conventional antidepressant agents. In addition, the terms "subject is in need of the prevention or treatment of a psychiatric disorder or a psychiatric disorder-related symptom" mean any subject who requires a reduction in the side effects of a conventional antidepressant agent. Furthermore, the terms "subject is in need of the prevention or treatment of a psychiatric disorder or a psychiatric disorder-related symptom" mean any subject who requires improved tolerability to any conventional psychiatric disorder treatment agent for psychiatric disorders therapy.

[0278] The present invention encompasses the prevention and/or treatment of any pychiatric disorder including, but not limited to, depression (uni-polar disorder or major depressive disorder), manic depression (bipolar disorders), anxiety disorder, anxious depression, panic disorder, attention deficit disorder, attention deficit/hyperactivity disorder,

melancholia (endogenous depression), depressive pseudodementia, dysthymic disorder, cyclothymic disorder, somatization disorder, conversion disorder, hypochondriasis, pain disorder, posttraumatic stress disorder, acute stress disorder, obsessive compulsive disorder, premenstrual dysphonic disorder, body dysmorphic disorder, schizophrenia, autism, agoraphobia, specific phobias, social phobia, acute stress disorder, dissociative amnesia, dissociative fugue, dissociative identity disorder, depersonalization disorder, and any combination of the above.

[0279] In one embodiment, the present invention encompasses the treatment or prevention of depression.

[0280] In other embodiments, the present invention encompasses a kit for preventing or treating psychiatric disorders or any psychiatric disorder-related symptoms in a subject that is in need of such prevention or treatment, the kit comprising one dosage form comprising a Cox-2 inhibitor and a second dosage form comprising at least one antidepressant agent.

[0281] The following examples describe embodiments of the invention. Other embodiments within the scope of the claims herein will be apparent to one skilled in the art from consideration of the specification or practice of the invention as disclosed herein. It is intended that the specification, together with the examples, be considered to be exemplary only, with the scope and spirit of the invention being indicated by the claims, which follow the examples. In the examples, all percentages are given on a weight basis unless otherwise indicated.

EXAMPLE 1

[0282] This example shows the preparation of the Cox-2 inhibitor, celecoxib.

[0283] Step 1: Preparation of 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione.

[0284] Following the disclosure provided in U.S. Patent No. 5,760,068, 4'-Methylacetophenone (5.26 g, 39.2 mmol) was dissolved in 25 mL of methanol under argon and 12 mL (52.5 mmol) sodium methoxide in methanol (25%) was added. The mixture was stirred for 5 minutes and 5.5 mL (46.2 mmol) ethyl trifluoroacetate was added. After refluxing for 24 hours, the mixture was cooled to room temperature and concentrated. 100 mL 10% HCl was added and the mixture extracted with 4 x 75 mL ethyl acetate. The extracts were dried over MgSO4, filtered and concentrated to afford 8.47 g (94%) of a brown oil which was carried on without further purification.

[0285] Step 2: Preparation of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

[0286] To the dione from Step 1 (4.14 g, 18.0 mmol) in 75 mL absolute ethanol, 4.26 g (19.0 mmol) 4-sulphonamidophenylhydrazine hydrochloride was added. The reaction was refluxed under argon for 24 hours. After cooling to room temperature and filtering, the reaction mixture was concentrated to afford 6.13 g of an orange solid. The solid was recrystallized from methylene chloride/hexane to give 3.11 g (8.2 mmol, 46%) of the product as a pale yellow solid, having a melting point (mp) of 157°-159°C; and a calculated composition of C_{17} H_{14} N_3 O_2 SF_3 ; C, 53.54; H, 3.70; N, 11.02. The composition that was found by analysis was: C, 53.17; H, 3.81; N, 10.90.

EXAMPLE 2

[0287] This example illustrates the production of a composition containing celecoxib and an antidepressant agent, and of a pharmaceutical composition containing the combination.

[0288] An antidepressant such as sertraline may be supplied by any one of several commercially available preparations. One such preparation of sertraline is the trade name Zoloft® 100mg (NDC: 00049-4910-66)

available from the Roerig Division of Pfizer Inc, NY, NY. Each tablet of Zoloft® contains 100mg of sertraline.

[0289] Alternatively, one of skill in the art may synthesize sertraline from a reading of the general synthesis outline disclosed in U.S. Patent Numbers 4,536,518 and 4,556,676.

[0290] A therapeutic composition of the present invention can be formed by intermixing sertraline, 100 g; and 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (200 g, as produced in Example 1, or as available from Pharmacia Corporation, Peapack, NJ, under the tradename Celebrex®), in a suspension or solution with a sterile pharmaceutically acceptable liquid.

[0291] After mixing, the combination of sertraline and celecoxib forms a therapeutic composition that is sufficient for the production of about 1000 human single dose units. Each single dose unit contains about 100 mg of sertraline and about 200 mg of celecoxib.

[0292] If desirable, a solid carrier and other materials may be intermixed with the therapeutic composition to form a pharmaceutical composition and the resulting pharmaceutical composition may be formed into capsules for human consumption, for example, by conventional capsule-forming equipment, where each capsule can contain about the same amount of the active ingredients as each of the single dose units of the liquid preparation described above.

[0293] Therapeutic and pharmaceutical compositions comprising a combination of any of the Cox-2 inhibitors alone and in combination with any of the sources of antidepressant agents that are described above can be formed by similar methods.

[0294] All references cited in this specification, including without limitation all papers, publications, patents, patent applications, presentations, texts, reports, manuscripts, brochures, books, internet postings, journal articles, periodicals, and the like, are hereby incorporated by reference into this specification in their entireties. The discussion of the references herein is intended merely to summarize the assertions made by

their authors and no admission is made that any reference constitutes prior art. Applicants reserve the right to challenge the accuracy and pertinency of the cited references.

[0295] In view of the above, it will be seen that the several advantages of the invention are achieved and other advantageous results obtained.

[0296] As various changes could be made in the above methods and compositions without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense. In addition, it should be understood that aspects of the various embodiments may be interchanged both in whole or in part.